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# BRITISH JOURNAL OF OPHTHALMOLOGY

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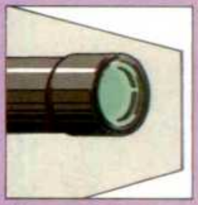

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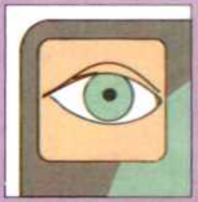

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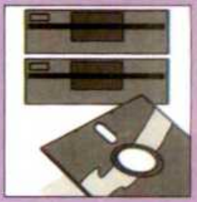

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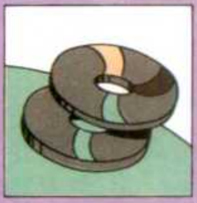

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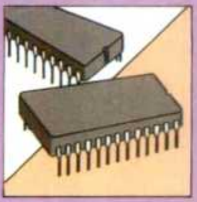

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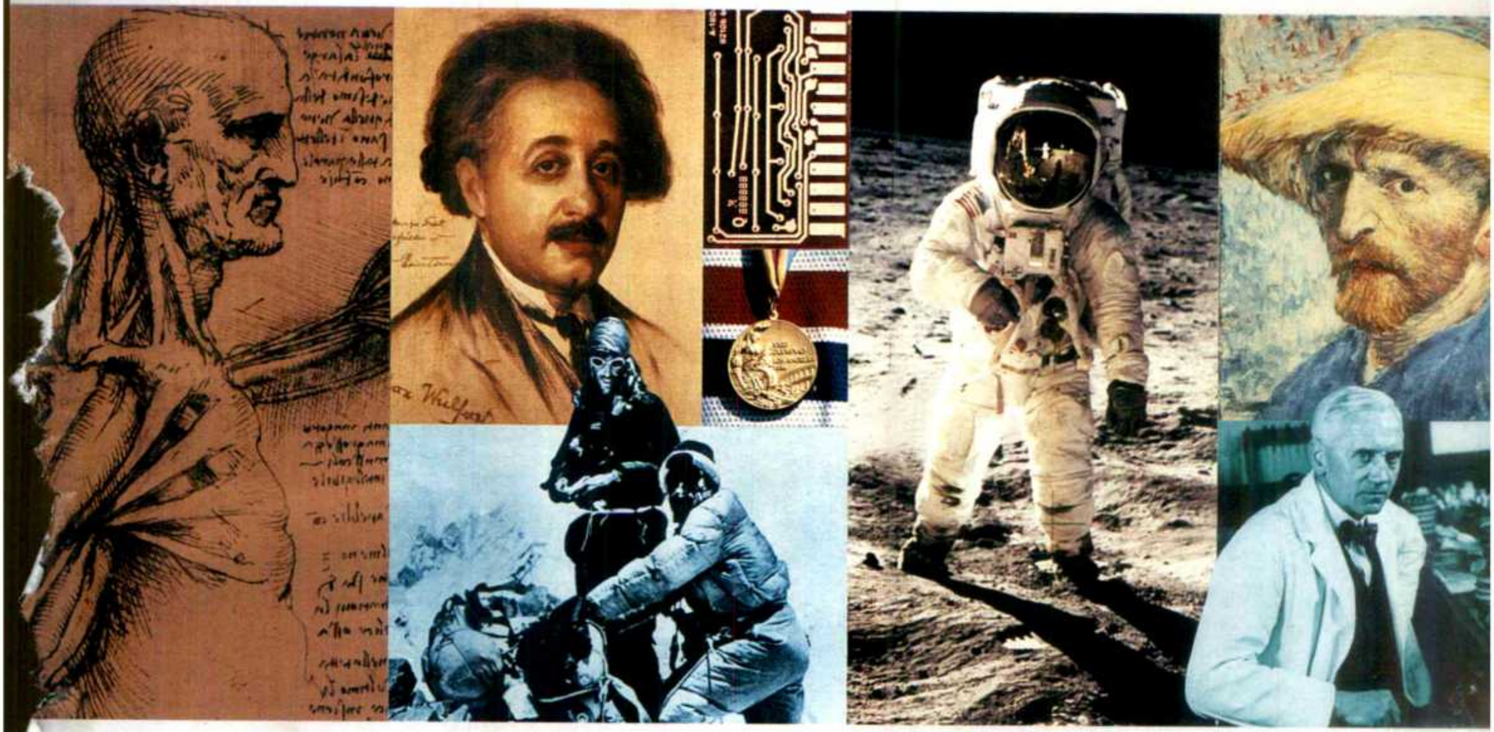

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*British Journal of Ophthalmology*, 1990; **74**: 1–2

BRITISH JOURNAL OF
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# *Editorials*

## The *BJO* in the 1990s

he *BJO* first came into existence in 1917 by the amalgama- on of the *Royal London Ophthalmic Hospital Reports*, which had first seen the light of day in 1857, the *Ophthalmic Review*, origin 1881, and the *Ophthalmoscope*, a relative newcomer from 1903.

Observant readers will have noticed minor changes in style and format from time to time. For example, the copies on my own shelves, dating back only to 1958, illustrate one obvious change, the alteration from across the page printing to double columns. This change was made in the 1975 volume and surprisingly arrived without any editorial comment. The external appearance was changed in 1978 when a plain orange cover was introduced and the contents were moved from the front to the back, in my view not a logical position – all right or an index but surely not for contents.

Now for the first issue of 1990 some more changes and we hope improvements are introduced. Readers of this issue will not need to be told that it is larger. It is in fact A4, a size which certainly fashionable though not everyone will agree uperior to the previous quarto (especially those like me who ave lovingly built their own bookcases to fit quarto volumes). Another change which it is hoped will be universally approved is the reinstatement of the contents on the front, where they should be. There are changes also in content. As well as the usual original articles there will now be a separate section for case reports. Case reports have always been a slight thorn in the editorial side – not that I dislike them. As a clinician I appreciate case reports as in some ways the life blood of a true clinical journal. What else does anyone expect from a journal with the pedigree of the *BJO*? What do the original *Royal London Ophthalmic Hospital Reports* consist of? Not all case reports, naturally, but a pretty good ration of them. The reason why I have found case reports a slight problem is because there are quite a number of readers who regard them as inferior in some way to investigative articles. I believe this is not an entirely justified attitude but nevertheless I think I have some idea how it comes about. If a given issue of the journal contains, say, 16 or 17 articles, some readers feel that they have been almost defrauded if too many turn out to be case reports and not original articles. I am not sure that this is justified, but I think I can see the point. Henceforth, therefore, case reports will have a separate section to themselves and as before will be restricted in length, except in exceptional circumstances, to 600 words.

In addition mini reviews are being introduced. Usually written by the members of the editorial committee, they will cover a selection of topics during the year. Mini reviews will be about 1200 to 1500 words long and will be published in addition to the now regular shorter editorials, which will continue to focus mainly on one or more articles of that particular issue. The first of these reviews will be found in this issue.

Finally there are hails and farewells to be made to some members of the editorial committee. To those who are leaving, each after many years of meritorious service, we say sarewell and we cannot thank you enough. To those who are joining the committee we extend a warm welcome and look forward to your forthcoming contributions to the editorial input of our journal.

REDMOND SMITH

## Glaucoma: is there light at the end of the tunnel?

In this issue a paper reports the results of a long study of the natural history of primary open angle glaucoma at King's College Hospital in London. For many years the team in this unit, under the leadership of R Crick, has been patiently building up a bank of data in which two important components have been the visual field scores, derived chiefly from studies with the Friedman analyser, and the intraocular pressures of a large number of patients. The object of the study was to see how close a relationship there was between the pressures and the field loss in these patients. The authors found a fairly strong correlation between pressure and degree of field loss at presentation, as would indeed be expected. Patients with the higher pressures tended to have more field loss than those with lower, but the correlation coefficient was not high, only – 0·26, though statistically significant. In practical terms one could say that more high-pressure cases of glaucoma were seen than low-pressure cases of glaucoma, which would of course be in keeping with usual clinical experience.

One should perhaps insert a word of caution here. The patients had presumably all to be referred to the clinic at King's College Hospital in the first place. One therefore has to ask, How were they detected in the beginning, before they were referred? Was the emphasis on pressure or on visual field loss? If routine measurements of pressure were done in the predetection stage, were routine measurements of visual field also? Such questions may sound somewhat academic, but they are nevertheless highly relevant where the correlation coefficient is fairly low, as in this study. However, common sense and a practically unanimous opinion among ophthalmologists would persuade one to accept this correlation in spite of such slightly uncomfortable doubts.

But when we come to the correlation between field and pressure during the follow-up period the doubts increase and the situation begins to look distinctly uneasy. For what the study finds is that the correlation coefficient between field loss and pressure while patients are under treatment is very weak indeed, only $-0{\cdot}06$, and it is difficult to see how much nearer one can get to zero than that.

What does this mean to us as clinicians, as advisers, counsellors, and comforters to our patients? Are we going to have to admit to them that our ability to control their rate of visual deterioration is actually less than we have led them to expect of us in the past? Or are we going to continue with our optimistic attitude that all will be well provided they are strict about following the prescribed regimen of treatment? And, worse still, where do the surgical 'hawks' stand in the face of results like this? Are these results an argument for more surgery or for less? How do the histories of this group of patients compare if they are divided into those who had surgery and those who did not? This particular aspect was not dealt with in the present study, but it would be of interest to see such an analysis in future if it were possible to extract the figures from the data.

Like many papers on glaucoma which set out to answer a particular question the answer usually raises further questions. One fascinating proposition raised in the discussion is the possibility of subgroups existing within chronic simple glaucoma. This I have to say will be the subject of a future paper from a different group to be published in the *BJO* shortly. I wish I were able to say that all will be revealed, but I am afraid that would be putting it a little too strongly. However, some interesting data will be presented which may well help towards answering some of the difficult questions raised in the current paper.

REDMOND SMITH

*British Journal of Ophthalmology*, 1990, 74: 3–6

## ORIGINAL ARTICLES

# Association between intraocular pressure and loss of visual field in chronic simple glaucoma

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Accepted for publication 24 July 1989

## Abstract

**This paper reports the analyses on data from 747 patients with chronic simple glaucoma (CSG) recorded in the King's College Hospital glaucoma data base between January 1970 and February 1985, having a mean follow-up time of 5·1 years (mode 8 years) with the object of determining the relationship of intraocular pressure (IOP) and visual field loss in CSG. A highly significant negative relationship was found between the presenting visual field coefficient (FC) and the untreated IOP ($r=-0{\cdot}26$, $p=0{\cdot}0001$) – that is, the higher the IOP on detection, the worse is the visual field. A weak negative correlation was present between the change of FC per year and the treated IOP ($r=-0{\cdot}06$), $p=<0{\cdot}05$). At treated IOPs ≤18 mmHg visual field loss averaged 0·6 unit per year and for IOPs >18 mmHg the average loss was 1·2 units per year. The data confirm both the importance of a raised IOP in the causation of chronic glaucomatous visual field loss and the importance of reducing the IOP in patients with chronic simple glaucoma.**

The hypothesis that an elevated intraocular pressure (IOP) is a factor in chronic glaucomatous optic atrophy and that control of the IOP will exert a favourable influence on its progress is widely accepted. The evidence for this is mainly inferential and anecdotal, but it is compelling to the degree that clinicians feel that it would be unethical not to attempt this form of treatment. However, many ophthalmologists believe that, in spite of the reduction of IOP to normal levels, the deterioration in visual fields of patients with chronic simple glaucoma (CSG) continues and is little affected by treatment.

Our objectives in making this analysis were:

(1) To determine if a relationship could be demonstrated between the level of untreated IOP and the state of the visual field at presentation in order to answer the question: Are higher untreated IOPs in chronic simple glaucoma associated with more visual field loss?

(2) To determine if a relationship could be demonstrated between the rate of visual field deterioration and the level of the treated IOP, or the extent to which IOP is lowered and the rate of visual field deterioration, in order to answer the question: Is it worth treating chronic simple glaucoma by reducing the IOP?

## Patients and methods

The King's College Hospital glaucoma database was initiated in 1969 with the object of improving patient care and of prospectively exploring the relationship of IOP and other factors to the progress of visual field loss in chronic simple glaucoma and ocular hypertension.[1] This analysis concerns data on 747 patients unselected other than by the requirement that they have CSG entered into the database between January 1970 and February 1985 and followed up for between 1·02 and 12·78 years (mean 5·1 yr, mode 8 years). Their median age was 70·25 years, with a range of 18–94 years. Visual field data were provided by the Friedmann Visual Field Analyser and were entered by the 'field cross' method. This involves dividing the 0–30° field into quadrants. Each quadrant is further divided into three zones which are 0–10°, 10°–20°, and 20°–30° from the fixation point containing 2, 4, and 3 test loci respectively. The resulting mean threshold sensitivity at all the loci tested was expressed as a visual field coefficient (FC),[2] for which at age 60 or older a maximum score was taken as 50 FC units (each FC unit=$(4\ \mathrm{dB}+1)\times 10$). 50 FC units is equivalent to an average threshold of 1·6 log units on the Friedmann instrument.

The annual field loss for each patient was calculated by regressing the field coefficient at each follow-up visit against the time since entry into the study.

For analyses using the annual field loss the following exclusions were applied: (1) patients with less than two dated follow-up visual field records; (2) patients with less than one year between first and last follow-up visual fields; (3) eyes showing an annual field loss of >10 FC or a gain of >13 FC units. (The distribution of the annual changes was examined to detect gross outliers. These outliers, as defined above, were omitted in accordance with standard practice with large data sets such as this. Outlying values of this type have an undue and possibly misleading influence on the statistical results.)

Changes in FC were expressed as the mean of the slopes of the individual patients. The Pearson correlation coefficient was used for all calculations except for that on the relationship between mean follow-up IOP and FC slope, for which the Kendall correlation was used. The Kendall correlation coefficient is more reliable than the Pearson when many outlying data points exist, as proved to be the case.

TABLE I *Mean untreated IOP and mean follow-up IOP: CSG worse eye*

| *IOP (mmHg)* | *n* | *Mean* | *SD* |
|---|---|---|---|
| Untreated IOP | 595* | 29·3 | 10·4 |
| Follow-up IOP | 566† | 18·9 | 4·1 |

*The untreated IOP was not available for 152 patients.
†A further 29 patients were excluded because they did not meet the follow-up criteria with regard to field coefficient measurements.

A *worse eye* analysis has been used, and this was defined by the presenting field coefficient. The measurements and disease code for that eye have then been used in the subsequent analyses. In the case of equality the right eye was used. Patients with no presenting FC for either eye were excluded, leaving 747 patients who could be included in the worse eye follow-up analysis.

## Results

The first analysis undertaken was the relationship between untreated IOP and the visual field coefficient (FC) at presentation.

The mean untreated IOP for 595 patients on whom this information was recorded was 29·3 mmHg and the mean follow-up IOP 18·9 mmHg (Table I). In spite of a manual search of original hospital notes the untreated IOP was not available for 152 patients. These patients were already on treatment when entered in the database, and the original Goldmann applanation reading was not known with certainty, so they were excluded. The majority of patients (66%) had been on treatment for less than one year prior to being entered into the study population. Figure 1 is a scatter plot of presenting IOP and initial field coefficient. The Pearson correlation coefficient between presenting IOP and initial FC was calculated and showed a highly significant negative relationship ($r=-0{\cdot}26$, $p=0{\cdot}0001$), demonstrating that at presentation the higher the IOP the worse the visual field. The mean initial and final FCs were calculated, and these are shown in Table 2. In order to relate final mean FC to initial mean FC and untreated presenting IOP, these were plotted in Figure 2. Patients whose presenting FC was zero were excluded from this figure. The relationship between a high presenting IOP and a poor visual field both initially and at the end of follow-up is demonstrated.

TABLE II *Mean initial and final field coefficients – CSG worse eyes*

| *Visual field coefficients* | *n* | *Mean* | *SD* |
|---|---|---|---|
| Initial FC | 747 | 24·9 | 15·6 |
| Final FC | 566 | 21·2 | 15·7 |

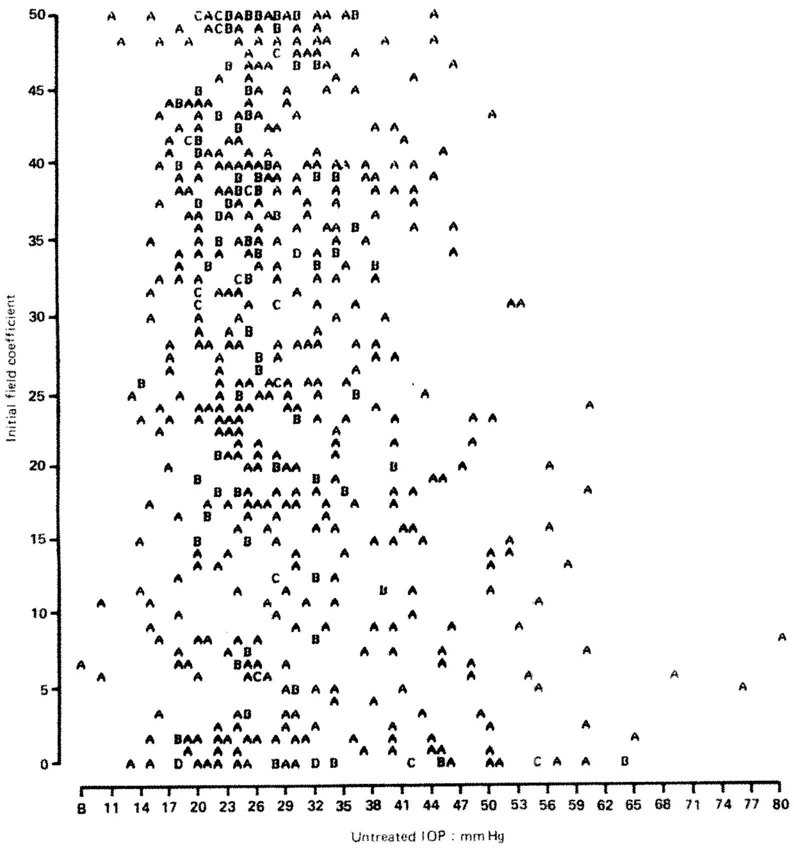

*Figure 1: Scatter plot of untreated IOP and initial field coefficient – CSG worse eyes. More than one observation may fall on any point. Thus A = 1 observation, B = 2 observations, etc.*

The mean follow-up IOPs were divided into six categories: ≤14 mmHg, >14 but ≤16 mmHg, >16 but ≤18, >18 but ≤20, >20 but ≤22, and >22 mmHg. The mean annual field loss within these six categories for worse eyes with CSG are shown in Figure 3. The higher mean follow-up IOPs showed greater rates of annual visual field loss, supporting the view that treatment to lower IOP *is* beneficial in retarding visual field deterioration in CSG. The mean follow-up IOP and the slope of the FC also showed a weak but significant negative relationship (Kendall correlation $r=-0{\cdot}06$, $p<0{\cdot}05$), thus confirming the above finding.

The doubling in rate of annual field loss between the group with 14≤16 mmHg and those with >22 mmHg has considerable potential clinical importance. The high rate of visual field loss seen in the 22 patients with a mean follow-up IOP of ≤14 mmHg in their worse eye was due to the fact that this category contained many eyes with complicated surgical histories following years of failed treatment. Several eyes had complications such as progressive cataracts, central vein occlusion, bound down pupils, persistent choroidal detachment, etc.

It was also noted that the lower the initial FC value the greater the difference between untreated and mean follow-up IOP (Pearson correlation coefficient, $r=-0{\cdot}09$, $p=0{\cdot}04$). This might imply that those with more damaged fields were treated more vigorously, which is an expected clinical reaction. Those with low initial FCs (who had higher presenting IOPs) necessarily required a greater fall in IOP to bring the IOPs down to acceptable levels.

## Discussion

Leydhecker[1] summarised the evidence for the role of an elevated IOP in the genesis of atrophy and excavation of the optic disc. This relationship has been questioned intermittently from the middle of the 19th century. Conversely the presence of an appreciably raised IOP without

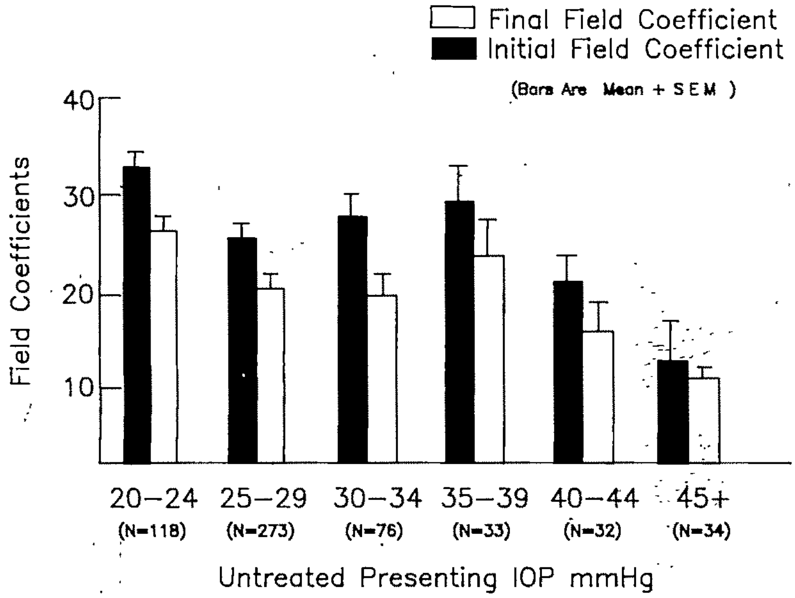

*Figure 2: Mean initial and mean final field coefficient versus untreated presenting IOP – CSG worse eyes. (This considers only these 566 eyes with both initial and final field coefficients recorded.)*

evidence of optic disc impairment over a considerable period of time has also been recognised.

It is generally accepted that the optic nerve damage in CSG may depend on several factors, including a raised IOP,[4-8] heredity,[9,10] myopia,[11,12] race,[13,14] sex,[7,15] diabetes,[16,17] vascular insufficiency and anaemia,[18,19] and other risk factors yet to be discovered.

The importance of IOP as a factor continues to be a matter of controversy. Leydhecker has made a strong case both for the influence of raised IOP in the causation of chronic glaucomatous optic atrophy and for the beneficial effect of the reduction of IOP on the retardation or arrest of optic nerve damage and therefore of visual field deterioration, reducing the IOP to really low levels if necessary.

Niesel and Flammer[20] showed in CSG that a significant correlation exists between the standard deviation of the variation of IOP annually and the development of field defect, but they did not find that the relationship between the mean level of pressure itself and field loss reached statistical significance. Their findings were based on a group of 33 patients with CSG followed for 11 years.

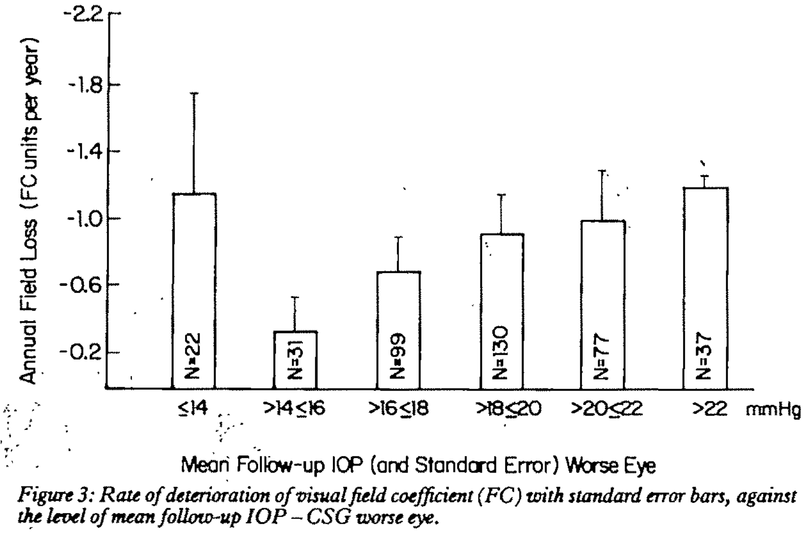

*Figure 3: Rate of deterioration of visual field coefficient (FC) with standard error bars, against the level of mean follow-up IOP – CSG worse eye.*

Krakau[21] considers 'that the concept of pressure as the generally valid cause of damage in chronic glaucoma is a hypothesis and not an established fact' but agrees 'that very high pressures are deleterious beyond doubt'. Sponsel *et al*[22] have also questioned the importance of the role of intraocular pressure in the aetiology of the optic atrophy of chronic simple glaucoma. Bengtsson[23] has highlighted the problem of low tension glaucoma (LTG) in his patients and regards it as being quite frequent. Most ophthalmologists, however, have found that very careful investigation of cases of suspected LTG results in only a small minority of patients being so classified. Bengtsson[24] also considers that the 'optic neuropathy of glaucoma is due to small vessel disease and not to a low perfusion pressure' and that 'the increase of IOP is an effect rather than a cause of glaucoma'. Treatment by lowering IOP, he claims, is based on obsolete ideas and has never been shown to be justified by any positive effect. As they are presented these views would appear to be lacking good supporting evidence, though the concept of a combination of raised IOP, a varying degree of ischaemic neuropathy, mechanical vulnerability of wide optic cups to pressure, weakness of connective tissue supporting the optic nerve head (for example, as in myopia), and possibly a weakness or abiotrophic tendency of the neural tissue itself as variable components of a 'primary open angle glaucomatous complex', is compatible with clinical observation and would be a useful unifying hypothesis for CSG, ocular hypertension, and low tension glaucoma.[25]

The results of this analysis show in this unselected population a very clear relationship between the untreated IOP and the extent of visual field loss at presentation. This in itself is support for the need to control IOP in patients with glaucoma. The clearest picture of this relationship will exist only at this point, since subsequent reduction in the IOP by therapy should make it increasingly difficult to demonstrate the negative relationship in the sampled population as a whole, though categorical analysis (Fig 3) may still show the same relationship at higher follow-up IOPs. This is indeed what we found.

It may also be expected that any benefit from lowering IOP would be revealed by a higher rate of visual field deterioration prior to presentation compared with that which occurred during the period of treatment. Inevitably we have no data on the annual change in FC prior to detection, and only a randomised trial involving a large group of CSG patients as untreated controls would provide evidence of the effect of IOP reduction. But in view of the existing clinical evidence for efficacy of treatment this may be ethically unacceptable.

Our data suggest (Fig 2) that a true IOP/field loss relationship may be more evident at pressures in excess of 39 mmHg, suggesting the possible existence of subgroups within CSG. IOP may not be the *dominant* influence in the pathogenesis of visual field loss in glaucoma until pressures in excess of 39 mmHg occur. It can be hypothesised that the patients with only moderately raised IOPs, that is, 20–35 mmHg, have a greater vascular or other element to their glaucomatous field loss than those with a much higher IOP.[25 26] Although we recognise that the correlations between the increasing field loss and IOP are weak and that the statistical significance of the correlation relies heavily on the large sample size, the doubling of the annual rate of loss of field at a treated IOP over 22 mmHg compared with a treated IOP of >14≤16 mmHg has considerable clinical importance.

The apparently divergent views of Leydhecker, Krakau, Bengtsson, Greve, and Sponsel, previously mentioned, all appear to be endorsed in part by the findings of this analysis as representing different aspects of a complex problem. Further analysis is in progress to determine the influence of amplitude of variation of IOP and peak pressures on visual field loss in this series of patients, especially in view of Niesel and Flammer's[18] observations.

## CONCLUSIONS

We have shown from this analysis, firstly, that the higher the pretreatment IOP the worse is the visual field. Secondly, a negative relationship between IOP and visual field loss is present but is understandably less pronounced once treatment has been instituted. There was a tendency for patients with higher mean follow-up IOPs to lose field faster than those with a lower follow-up IOP. The relationship between treated IOP and continuing field loss does indeed exist but in this analysis was smaller than has hitherto been widely assumed. One reason for the weak relationship found was the poor visual field outcome in the small number (n=22) of patients with a treated IOP of ≤14 mmHg. Many of those patients had complicating factors unrepresentative of the rest of the population. Treatment to reduce the intraocular pressure is therefore important to prevent or reduce the loss of visual field in chronic simple glaucoma.

In practice it would be reasonable in an individual case to reduce the IOP progressively until deterioration of the visual field is arrested. If this cannot be achieved, factors other than IOP may be preponderant. Methods of treating the other factors may be revealed by further research, but in the present state of our knowledge reduction of the IOP is still undoubtedly the ophthalmologist's primary duty when managing chronic glaucoma.

The maintenance of the database involves extensive team work by all the members of the Department of Ophthalmology at King's College Hospital, and we are particularly indebted to Mr Roger Coakes, Dr Patricia Reynolds, Mrs Jean Curtis, and Mrs Eileen Cobb.

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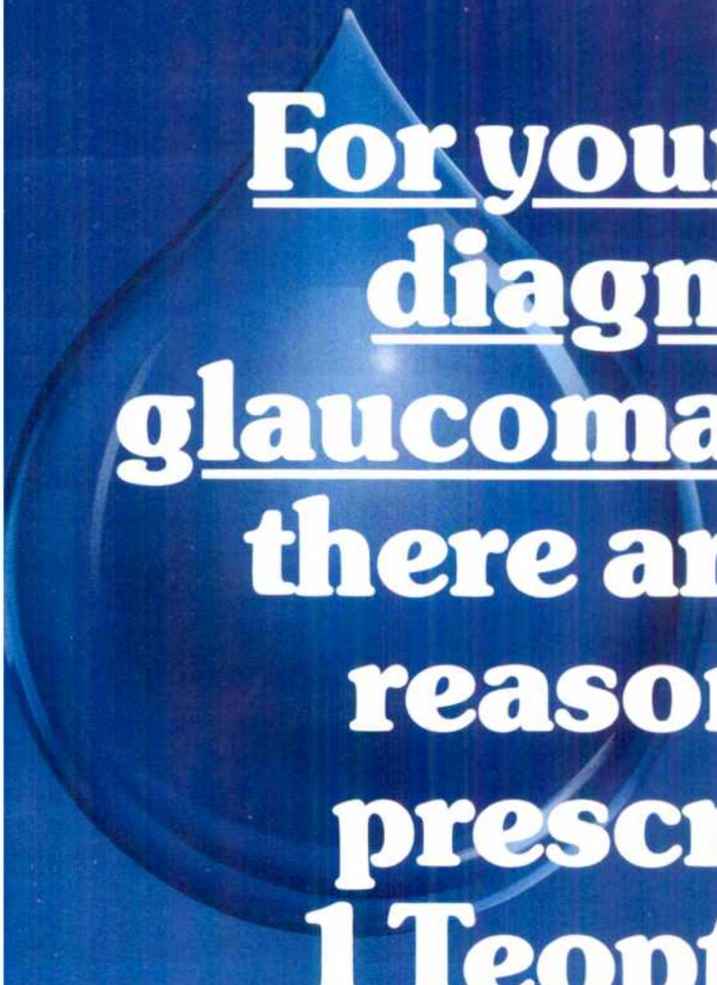

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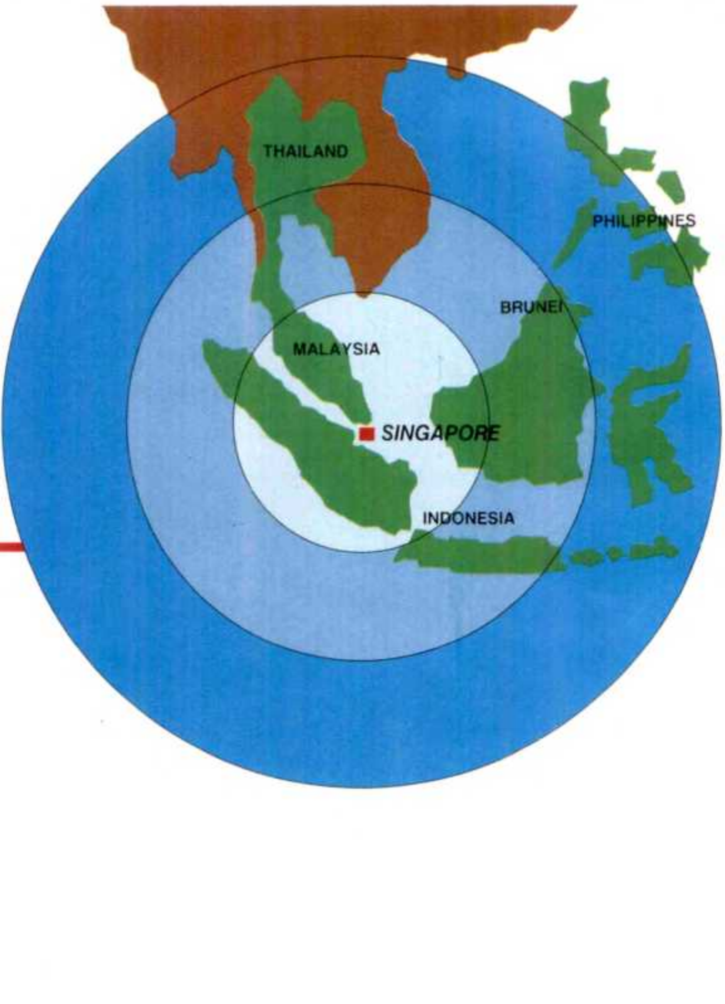

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# Effect of donor parameters on primary graft failure and the recovery of acuity after keratoplasty

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## Abstract

**A retrospective evaluation was made of 983 penetrating corneal grafts. Donor corneas stored in either K-Sol or McCarey-Kaufman media had a significantly greater rate of primary graft failure (about 2%) than those kept in moist chamber storage (0%). Selected subgroups of 50 corneas from each storage system were studied to determine the time taken to reach a postoperative acuity of 6/12. No significant correlation was found between this time and either the duration of storage of donor corneas or the age of donor. A significant delay in recovery of visual acuity was found with increasing age of recipient. The increased average time from donor death to surgery for K-Sol (56 hours) and McCarey-Kaufman (40 hours) corneas compared with moist chamber corneas (15 hours) facilitated the scheduling of surgery at the cost of increased chance of primary graft failure.**

Factors which increase the likelihood of success in penetrating keratoplasty include good quality donor material, minimal surgical trauma, and a favourable host environment. There is no simple measure of donor tissue quality. Many surgeons are influenced in their choice of material by such attributes as the age and the time elapsed since donor death. It is commonly believed that the best results, in terms of early graft clarity, are obtained by using corneas from young donors with minimum delay after death. However, in one series of nearly 400 cases no significant difference in subsequent graft clarity was found between donors grouped into four age bands (from under 50 years to over 70 years old).[1] Similar results were seen in the Australian Graft Registry; in nearly 500 cases the probability of graft survival was almost identical irrespective of donor age of less than 50 years or greater than 70 years.[2] The Australian Graft Registry also reported that storage of corneas in McCarey-Kaufman medium for as long as five days had no effect on subsequent graft survival. The duration of corneal storage (of up to three days in McCarey-Kaufman medium and up to a few weeks in organ culture) was unrelated to the postoperative visual acuity in one small series.[3] The use of storage media allows time for tissue typing for matched grafts, screening of donor serum for viral antibodies, and for optimum scheduling of surgery.

The use of storage media involves extra handling of the donor cornea and subjecting it to a change of environment. It is possible that this may result in an increased rate of primary graft failure compared with moist chamber storage. It is also possible, however, that storage media are truly preservative. Perhaps eyes in moist chamber storage should be transferred to a storage medium even if their use is envisaged within a few hours. Media that contain chondroitin sulphate, such as K-Sol,[4] appear to be more effective at maintaining higher levels of adenosine triphosphate (ATP), necessary for the cornea to remain viable, than storage media without, such as McCarey-Kaufman, which in turn is more effective than moist chamber storage.[5,6] In animal experiments[7] and in vitro with human corneas[8] K-Sol appears to be superior to McCarey-Kaufman medium in maintaining endothelial cell viability.

This study was designed to compare the rate of primary graft failure of corneas stored in K-Sol or McCarey-Kaufman media with those stored in a moist chamber. It also was designed to examine the possible relationship between the known donor cornea parameters, such as age of donor and method and time of storage, and the postoperative clinical performance of the cornea as represented by the time taken for recovery of visual acuity to 6/12.

## Materials and methods

A retrospective study was made of all corneal grafts performed at Moorfields Eye Hospital from January 1984 to October 1988. Until August 1985 the only method of storage used was the whole eye, moist chamber technique. At this time McCarey-Kaufman medium was introduced, and then in April 1987 a change was made to K-Sol. Donor corneas were all examined with a slit-lamp and most had endothelial specular microscopy before they were passed as being suitable for storage in McCarey Kaufman or K-Sol Media.

The incidence of primary graft failure was determined for all 983 patients. This was diagnosed when, in the absence of an identifiable cause such as glaucoma or rejection, a graft remained oedematous and failed to show any postoperative recovery of function.

For the assessment of the recovery of visual acuity strict exclusion criteria were employed. These were designed to minimise, as far as possible, the influence of factors other than corneal clarity on the recovery of visual acuity. Eyes were excluded from the study if there was known to be any noteworthy preoperative path-

TABLE I *Numbers of primary graft failures*

| | *Number (%) of patients* | | |
|---|---|---|---|
| *Graft patients* | *Moist chamber* | *McCarey-Kaufman* | *K-Sol* |
| Selected 50 patients | 0/50 (0) | 1/50 (2·0) | 3/50 (6·0) |
| All graft patients | 0/278 (0) | 4/224 (1·78) | 10/481 (2·07) |

TABLE II *Summary of findings in primary failure grafts*

| *Case* | *Storage* | *Recipient age (years)* | *Recipient diagnosis* | *Donor age (years)* | *Time from death to storage (hours)* | *Time in storage (hours)* |
|---|---|---|---|---|---|---|
| 1 | McCarey-Kaufmam | 23 | Keratoconus | 77 | 21 | 25 |
| 2 | McCarey-Kaufman | 64 | Lattice dystrophy | 73 | 9 | 48 |
| 3 | McCarey-Kaufman | 51 | Pseudophakia | 67 | 12 | 5 |
| 4* | McCarey-Kaufman | 30 | Measles keratitis | 61 | 13 | 21 |
| 5* | K-Sol | 77 | Interstitial keratitis | 65 | 13 | 110 |
| 6* | K-Sol | 25 | Macular dystrophy | 69 | 19 | 67 |
| 7 | K-Sol | 72 | Pseudophakia | 69 | 19 | 72 |
| 8 | K-Sol | 68 | Traumatic scar | 70 | 23 | 90 |
| 9* | K-Sol | 62 | Fuchs dystrophy | 70 | 23 | 117 |
| 10 | K-Sol | 60 | Pseudophakia | 40 | 21 | 48 |
| 11 | K-Sol | 85 | Pseudophakia | 67 | 17 | 158 |
| 12 | K-Sol | 63 | Fuchs dystrophy | 59 | 2 | 67 |
| 13 | K-Sol | 72 | Fuchs dystrophy | 72 | 14 | 77 |
| 14 | K-Sol | 40 | Keratoconus | 27 | 32 | 51 |

*These patients were from the study groups of 50 patients.

ology in the recipient apart from corneal opacity. Eyes with corneal vascularisation, poor tear film, corneal perforation, or with pre-existing glaucoma or retinal pathology were excluded. Eyes that had intracapsular cataract surgery performed at graft surgery were excluded, as this procedure is known to be associated with a high incidence of cystoid macular oedema,[9] but eyes that had extracapsular cataract surgery, with or without lens implant, at the time of corneal graft were included.

Eyes were also excluded from this part of the study if conditions likely to affect visual acuity were noted after graft surgery, such as retinal detachment, cystoid macular oedema, or glaucoma. This 'retrospective' exclusion of cases is justifiable because these complications cannot be related to the donor cornea parameters.

After these exclusions the first 50 grafts from each of the three storage methods were included in the recovery of vision study. For these 150 patients the time taken to reach a postoperative acuity of 6/12 (with refraction or with the use of a pinhole) was recorded. Other recorded details included donor and recipient ages, time to storage, and time from storage to surgery, the use of viscoelastic material (2% hydroxypropylmethylcellulose or sodium hyaluronate), and whether surgery was performed by a consultant or by a resident. Hospital notes were also examined to find patients who had visual acuities recorded, at successive clinic visits, with the use of a pinhole and with refraction. These visual acuities, and the interval between them, were recorded in order to compare these two techniques of optical correction.

## Results

Table I shows the incidence of primary graft failures, both for the total number of grafts (278 moist chamber, 224 McCarey Kaufman and 481 K-Sol) and for the selected subgroups (each of 50 patients). There was no statistical difference between the three storage systems for the subgroups, but over the total number of grafts the rate of primary graft failure was significantly greater both for McCarey-Kaufman ($p<0·05$) and for K-Sol ($p<0·02$) storage media compared with the moist chamber group ($\chi^2$ test). Table II provides clinical details on the primary graft failures.

TABLE III *Indication for corneal graft*

| *Diagnosis* | *Number of patients** | | |
|---|---|---|---|
| | *Moist chamber* | *McCarey-Kaufman* | *K-Sol* |
| Keratoconus | 33 | 27 (1) | 24 |
| Age related corneal decompensation; Fuchs, pseudophakic, aphakic | 8 (2) | 5 (4) | 11 (2) |
| Corneal dystrophies; lattice, macular, granular, congenital hereditary | 2 | 6 | 7 (3) |
| Interstitial keratitis | 3 (2) | 4 (1) | 2 (2) |
| Others | 4 (2) | 8 | 6 |
| Total | 50 | 50 | 50 |

*Figures in brackets indicate number in each group where cataract surgery was performed at the time of corneal graft.

For the selected subgroups of 50 patients the average age of recipient was 40 years for the moist chamber group, 43 for McCarey-Kaufman group, and 45 for the K-Sol group. The average time from death to storage was eight hours (range one to 22) for moist chamber, 10 hours (range two to 26) for McCarey-Kaufman, and 11 hours (range two to 23) for K-Sol. Surgery was performed by a consultant in 72% of the moist chamber group, 82% in the McCarey-Kaufman group, and 74% in the K-Sol group. These differences are not significant. Viscoelastic material was used significantly more often in both the McCarey-Kaufman (64%) and the K-Sol (54%) groups than in the moist chamber group (33%) ($\chi^2$ test, $p<0·02$). The average time from donor death to surgery was also different between the three groups: 15 hours (range one to 34) for moist chamber storage, 40 hours (range 10 to 102) for McCarey-Kaufman, and 56 hours (range 18 to 188) for K-Sol. Table 3 compares the preoperative diagnoses in these three subgroups of patients.

In 200 randomly selected clinic visits a refraction was performed 18 times, representing one refraction per 11 visits. Fifty four occasions were found when a pinhole acuity recorded at one clinic visit was followed by refractive acuity at the subsequent visit (on average 1·24 months later). On average this pinhole acuity was 0·46 Snellen line worse than the subsequent refractive acuity. Sixteen occasions were found when a refractive acuity recorded at one clinic visit was followed by a pinhole acuity at the subsequent visit (on average 1·01 months later). This pinhole acuity was again, on average, worse than the refractive acuity, by 0·12 Snellen line. The refractions on these patients showed an average spherical error of 3·56 dioptres (range 0 to 12·75), with 4·99 dioptres of cylinder (range 0 to 10).

Figure 1 shows the recovery of visual acuity for each of the three selected subgroups. Each line plots the percentage of patients that, at a given time postoperatively, have achieved a visual acuity of 6/12. The plot is cumulative and does not show if a patient subsequently lost visual acuity. With the exception of the primary graft failures all eyes reached an acuity of 6/12. There was no significant difference between the three groups (log rank test). The mean time to 6/12 vision was 2·3 months for moist chamber, 2·6 months for McCarey-Kaufman, and 2·1 months for K-Sol. These differences are not significant.

Figures 2–4 show three scattergrams which plot the time to 6/12 vision against the time from donor death to surgery for each of the three

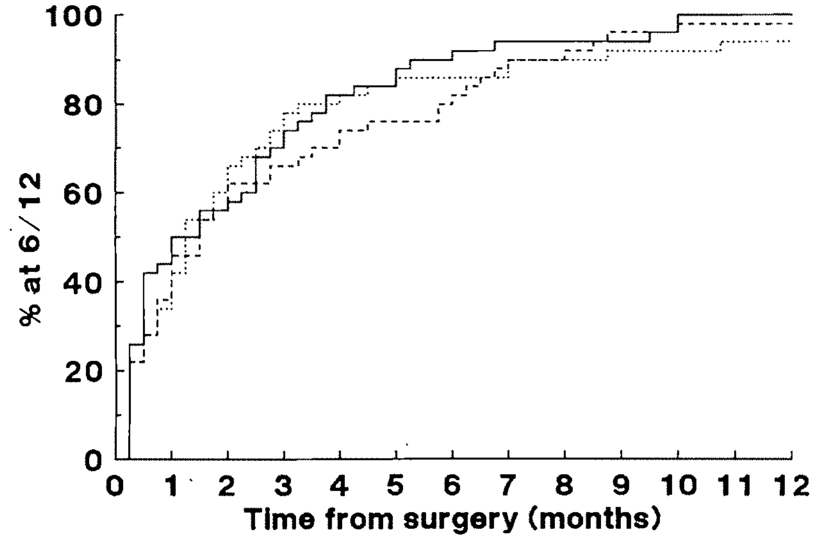

*Figure 1: Cumulative percentage of patients that have achieved a visual acuity of 6/12 plotted against time. Solid line represents moist chamber storage, dashed line represents McCarey-Kaufman medium, and dotted line represents K-Sol.*

storage systems. A linear regression line is shown on each scattergram, but in no case is the correlation significant; regression data are shown in Table 4. The negative slope for the moist chamber and McCarey-Kaufman plots indicates a (non-significant) reduced time to 6/12 vision with longer storage times. For the K-Sol group the positive slope indicates a (non-significant) delay to 6/12 vision of three days for every extra 24 hours that the cornea is kept in storage.

It is possible to make a direct comparison between the three storage techniques by considering donor eyes that were used between 18 and 34 hours after death. This time interval was common to all three storage techniques; 18 hours was the shortest period for K-Sol and 34 hours was the longest period for a moist chamber donor. Over this interval 18 moist chamber, 15 McCarey-Kaufman, and 16 K-Sol stored corneas were used. There was no significant difference in average time to 6/12 vision between these cases.

Figure 5 is a scattergram which plots the time to 6/12 vision against age of the donor. Testing the three groups separately shows no significant correlation between time to 6/12 vision and age of donor. Linear regression analysis on all three groups pooled shows no significant correlation (slope 0·0094, intercept 1·94, correlation coefficient 0·061). This slope indicates a (non-significant) delay in time to 6/12 vision of 0·28 days for each additional year of donor age. To examine the hypothesis that donors over the age of 60 may show a greater trend to poorer quality, linear regression analysis was repeated taking only those donors over the age of 60. This again showed no significant correlation (slope −0·009, intercept 3·24, correlation coefficient −0·026). This slope indicates a (non-significant) reduction in time to 6/12 vision with increasing donor age over 60 years.

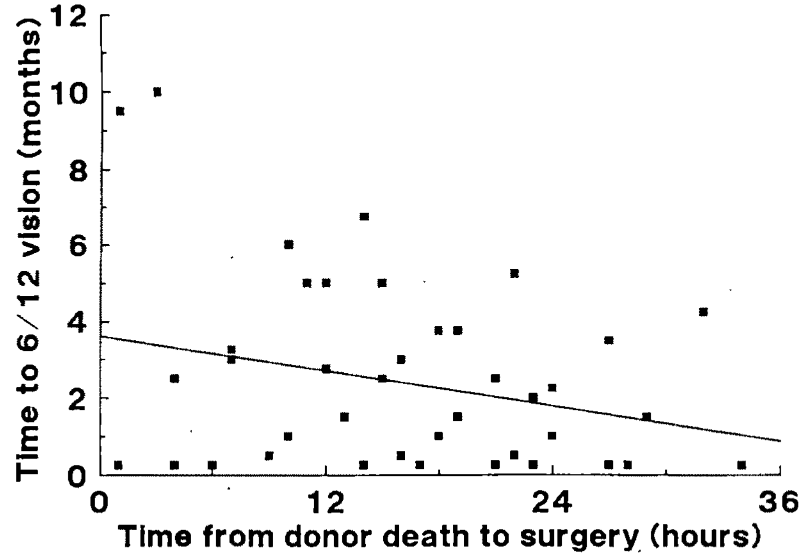

*Figure 2: Moist chamber stored corneas. Scattergram of time to 6/12 vision versus time from donor death to surgery. The linear regression line shown is not significant.*

Figure 6 is a scattergram which plots the time to 6/12 vision against age of recipient. All three storage techniques are combined. Linear regression analysis showed a significant correlation ($p<0·025$, slope 0·027, intercept 1·17, correlation coefficient of 0·22). The slope of the regression line represents a (significant) delay in time to 6/12 vision of 0·83 days for each additional year of recipient age; a 20-year old patient may be expected to reach 6/12 vision six weeks earlier than a 70-year old. However, there was considerable overlap when confidence limits were considered; 95% of 20-year old patients may be expected to reach 6/12 vision between two and 14 weeks, whereas 95% of 70-year old patients took between three and 23 weeks.

## Discussion

Over the total of 983 grafts there was a significant increase in the rate of primary graft failure for corneas stored in either McCarey-Kaufman or K-Sol compared with those stored in a moist chamber. Over the selected 150 patients the rate of primary graft failure was greater in the media stored corneas, but this did not reach statistical significance. There was no difference in the rate of primary graft failure between the two media; each was associated with an incidence of about 2%. In this series there were no primary graft failures in moist chamber stored corneas.

This superiority of moist chamber storage should be interpreted with caution. On average, McCarey-Kaufman and K-Sol corneas were stored respectively 2·6 and 3·7 times as long as moist chamber corneas; it may well be that even higher rates of failure would be associated with moist chamber storage over these lengths of time. It may be noted that viscoelastic material was used more often with the media stored corneas than with moist chamber corneas.

If the increased rate of primary graft failure with media storage reflects decreased endothelial cell viability, then it seems possible that such corneas may be slower to recover clarity, and so perhaps visual acuity, postoperatively. No such association was found; there was no significant difference between the three subgroups in either average time to 6/12 vision or in the pattern of recovery, as shown in Figure 1. It may also be postulated that prolonged donor storage times and increased donor age should result in decreased endothelial cell viability and slower visual recovery. However, no significant correlation was found between the time to 6/12 vision

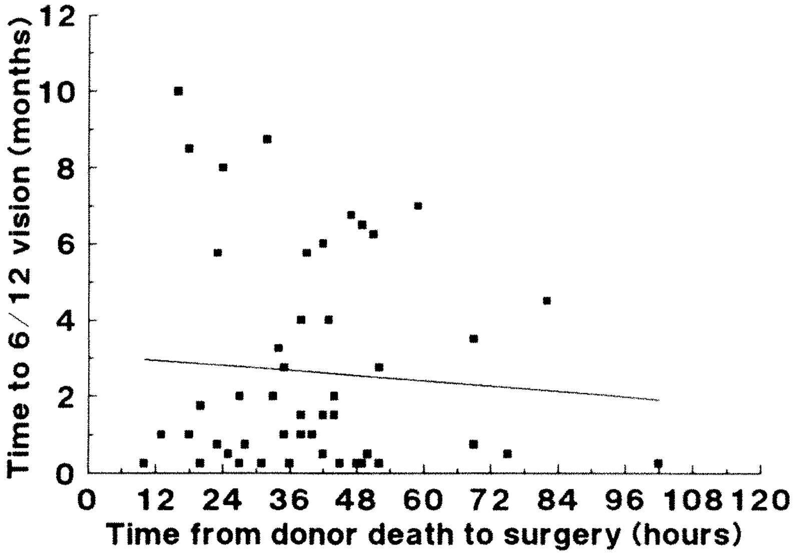

*Figure 3: McCarey-Kaufman stored corneas. Scattergram of time to 6/12 vision versus time from donor death to surgery. The linear regression line shown is not significant.*

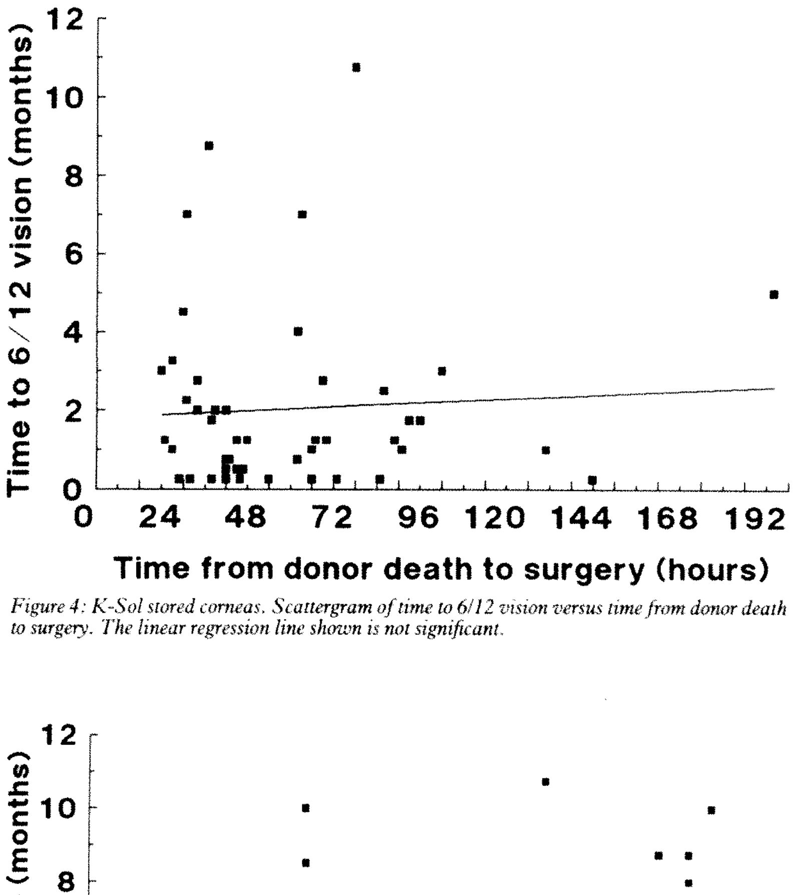

*Figure 4: K-Sol stored corneas. Scattergram of time to 6/12 vision versus time from donor death to surgery. The linear regression line shown is not significant.*

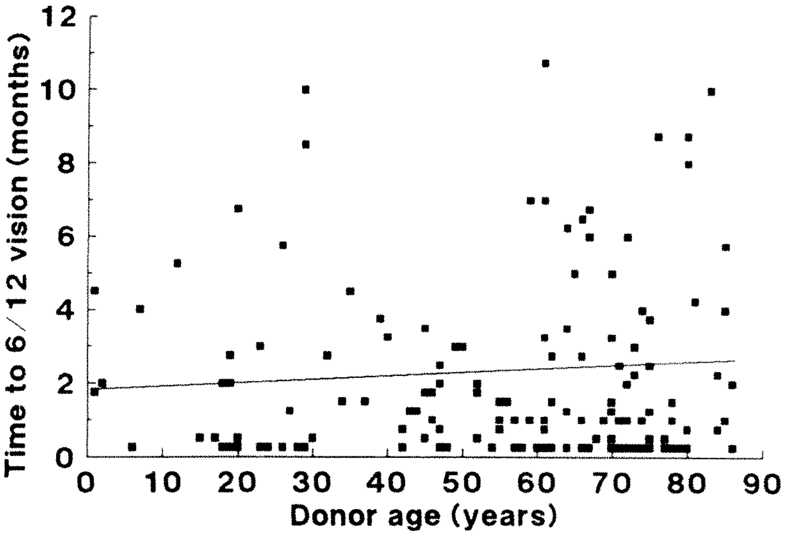

*Figure 5: Scattergram of time to 6/12 vision versus age of donor. The linear regression line shown is not significant.*

TABLE IV *Regression data for Figure 2; months to 6/12 vision versus hours in storage*

| | *Regression data* | | | |
|---|---|---|---|---|
| *Storage type* | *Slope* | *Intercept* | *Correlation coefficient* | *Significance* |
| Moist chamber | −0·075 | 3·60 | −0·258 | NS |
| McCarey-Kaufman | −0·011 | 3·08 | −0·075 | NS |
| K-Sol | +0·004 | 1·81 | +0·063 | NS |

NS = not significant.

and either the time from death to surgery (Figs 2–4) or the donor age (Fig 5).

Prolonged storage does reduce endothelial cell density,[10] and it is likely that endothelial cell viability is also affected by storage technique and donor age. The chosen clinical endpoint in this study, time to 6/12 vision, is presumably not sensitive to such differences.

Although visual acuity is not a sine qua non of a functioning graft, it is usually true that an eye with good acuity has a successful, functioning graft. In this study visual acuity was used as a measure of graft quality. Patients who had additional pathology that could reduce acuity were excluded from the analysis. Good acuity does not, however, predict continuing graft success. Normal corneas have endothelial cell function in excess of that required to maintain corneal deturgescence and clarity. Techniques of storage and donor parameters that adversely affect endothelial cells may not reduce function below the critical value. An initially successful graft may, over a longer period of follow-up, lose clarity and fail.

Pinhole or refractive acuities were both considered satisfactory endpoints in this study. The large refractive errors often present in these patients resulted in poor unaided acuities which did not accurately reflect the corneal clarity. Unfortunately pinholes not only overcome refractive error,[11] but they may also improve visual acuity in the presence of corneal irregularity and minor opacity. There therefore exists the possibility that the pinhole acuities recorded in this study presented an overoptimistic assessment of corneal clarity. The data showed, however, that the pinhole acuities were close to the refractive acuity (on average, within 0·38 Snellen lines). Pinhole acuities were actually slightly worse than refractive acuities, especially if the pinhole acuity was recorded at the visit before rather than the visit after the occasion when refraction was performed. The reduction in acuity measured with pinhole was more marked (0·46 Snellen lines) if the pinhole acuity was recorded before a refraction than when it was recorded after refraction (0·12 Snellen line). This difference may be explained by assuming that, with increasing postoperative time, corneal clarity improves and so allows the better acuity at the later date. For the pinhole acuity measured after refraction the small reduction in recorded acuity presumably represents the failure of the pinhole fully to correct the refractive error.

Donor cornea quality may also be assessed in vivo by measurements of corneal thickness and endothelial cell density. However these parameters do not provide an absolute standard by which the success of a graft may be judged.

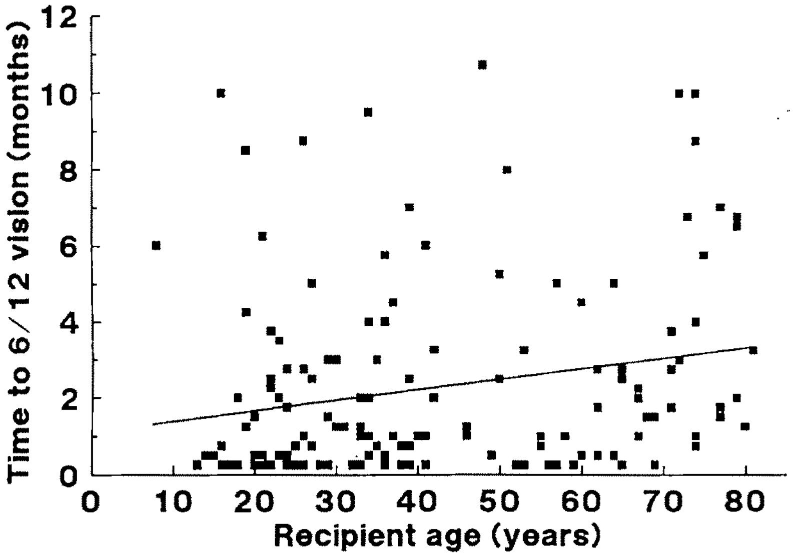

*Figure 6: Scattergram of time to 6/12 vision versus age of recipient. There is significant correlation as shown by the linear regression line.*

Individual grafts that are equally satisfactory from a clinical point of view may show wide variation in these measures. Laboratory based tests of corneal function can provide a basis by which various cornea storage techniques can be evaluated,[5-8] but an ideal clinically applicable method of assessing endothelial cell viability has yet to be developed.[12] In our patients further follow-up may provide information on long term decompensation and may show, for example, an increased rate of late failure in grafts from older donors.

Patients in this study showed a very wide variation in the time that was taken to reach a postoperative acuity of 6/12. No significant correlation was found with the known donor parameters, but there was a significant delay in recovery of vision with increasing recipient age. However, this accounted for only a very small part of the variation in time to 6/12. Other factors, not identified here, such as reduced macular function in the elderly may be important. Improved techniques are needed to assess both donor corneas and also more of the variable host factors, such as inflammatory response and the presence and time course of cystoid macular oedema.

Although this study failed to find clinical advantage in using corneas from younger donors or from corneas stored for shorter periods in any one storage system, such corneas remain theoretically preferable. The use of McCarey-Kaufman and K-Sol storage media, with the associated increased time of storage, facilitated the scheduling of surgery, but were associated with an increased risk of primary graft failure.

We thank Darwin Minassian for his statistical analysis and the surgeons of Moorfields Eye Hospital for permission to report their cases.

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# Reliability of photographs for grading trachoma in field studies

Sheila K West, Hugh R Taylor

## Abstract

**The validity and reliability of the use of photographs to assess active trachoma and scarring was studied in a village where the disease was hyperendemic. One hundred and thirty six subjects were graded clinically and had photographs taken of the upper tarsal plate. Agreement between the clinical grade in the field and the grade on the photograph was very good for follicular trachoma, severe trachoma, and scarring ($\kappa$ statistic values were 0·71, 0·74, and 0·73 respectively). In field studies photographic documentation of trachoma appears to be a valid and reliable approach.**

Trachoma, a chronic conjunctivitis caused by *Chlamydia trachomatis*, is a major cause of blindness for much of the developing world.[1] The assessment clinically of its presence and severity has until recently been difficult because of the lack of a reliable grading scheme. The World Health Organisation published a new, simplified grading scheme[2] which has been shown to give reproducible trachoma grading among ophthalmologists and ophthalmic nurses after appropriate instruction.[3] This grading scheme has been used in cross-sectional surveys of risk factors for trachoma[4] and is being assessed for its utility in longitudinal assessments of change in trachoma over time.

However, relying on the clinical assessment of a longitudinal change in trachoma may be less than optimal for several reasons. First, the clinical examiner may be aware of which subjects have received a specific treatment, and this may subconsciously bias his grading. Secondly, the grader may be aware of the initial grading at the time of follow-up. Thirdly, clinical grading, even if done reliably at each time point, may drift over time in the absence of objective monitoring. For these reasons it might be advantageous to have photographic documentation of a subject's trachoma status at each time; the photographs could then be graded at one time in a masked fashion. However, the reliability of using photographs to detect follicles, scars, and the inflammation of intense disease as defined by the new WHO grading scheme has not been shown.

The purpose of this study was to determine the reliability of a single photograph of the upper tarsus to reproduce the clinical findings as compared with the clinical grade by an experienced trachoma grader.

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## Methods

A series of 136 subjects in a trachoma endemic region of East Africa were graded clinically for the presence of follicular trachoma (TF), intense inflammatory trachoma (TI), and trachomatous scarring (TS) in accordance with the WHO new grading scheme.[2] This grading scheme has been shown to be reproducible when used to grade subjects clinically. In the previous study the $\kappa$ statistic indicating the intraobserver agreement was, on average, 0·74 for TF, 0·77 for TI, and 0·76 for TS.[3]

A photograph of the upper tarsal plate for the right and left eye of each subject was taken with a single lens reflex camera with a macro lens and Kodakchrome ASA 25 film which gave a 1:1 magnification. The film was developed by Kodak Central Laboratories in Rockville, MD. Each subsequent slide was graded by one of us (HRT) who had clinically examined each subject; he was unaware of the original clinical grades assigned to the eye. Photographs were graded by placing them on an illuminated box and observing them with a 2·5× loupe.[5]

The signs of trichiasis (TT) and corneal opacity (CO) were not included in this study because these signs are not likely to change dramatically in most people over a relatively short time. The signs which can fluctuate indicate active trachoma (TF, TI) and scarring (TS).

All subjects gave verbal consent for the clinical examination and photography in accordance with approval by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institution. All subjects with active severe trachoma were treated after examination.

The data were entered into an IBM-AT computer and analysed by a $\kappa$ statistic to assess the percentage agreement, adjusted for agreement due to chance alone.[6]

## Results

Five subjects (4%) had bilateral photographs (10 eyes) which were ungradable. In three photographs the upper eye lid was not adequately everted. In four photographs the focus was bad or the flash reflex obscured the tarsal plate. In three photographs the examiner's hand shadowed the upper lid. Two of these five subjects had clinical grades of TF in both eyes, and three had scarring only (TS). An additional 13 subjects had one photograph which was ungradable, but the photograph of the companion eye could be graded. A total of 249 eyes were evaluated for agreement.

Agreement between the clinical grade and the photograph grade for follicular trachoma and scarring was very good, $\kappa$=0·71 and 0·73, respectively (Tables I and II). Agreement was more difficult to assess for severe disease because relatively fewer subjects in this series had severe trachoma (Table III). Thus, the high value for

TABLE I *Reliability of photograph grading for follicular trachoma (TF) in 249 eyes*

| | *Photograph grade* | |
|---|---|---|
| | *Present* | *Absent* |
| Clinical grade: | | |
| Present | 66 | 22 |
| Absent | 10 | 151 |

Percentage agreement=87%.
$\kappa$=0·71 (95% confidence interval=0·62, 0·80).

TABLE II *Reliability of photograph grading for trachomatous scarring (TC) in 249 eyes*

| | *Photograph grade* | |
|---|---|---|
| | *Present* | *Absent* |
| Clinical grade: | | |
| Present | 163 | 11 |
| Absent | 17 | 58 |

Percentage agreement=89%.
$\kappa$=0·73 (95% confidence interval=0·63, 0·82).

TABLE III *Reliability of photograph grading for trachomatous-intense (TI) in 249 eyes*

| | *Photograph grade* | |
|---|---|---|
| | *Present* | *Absent* |
| Clinical grade: | | |
| Present | 11 | 0 |
| Absent | 7 | 231 |

Percentage agreement=97%.
$\kappa$=0·74 (95% confidence interval=0·56, 0·92).

percentage agreement, 97% reflected the majority of negative findings. However, the $\kappa$ value, 0·74, shows very good agreement, and the 95% confidence interval includes values which are acceptable.

## Discussion

These data suggest that a single photograph of the upper tarsal plate can reliably reproduce the clinical findings of follicular trachoma and scarring. The agreement between the clinical grade and the grade in the photograph for the same subject was comparable to the agreement obtained if the same subject was graded clinically twice by the same observer.

It is worthwhile to note that the photograph grader identified TI in seven eyes where TI was not observed clinically. Reasons for this finding are not clear. The photograph grader had the time to peruse the photograph and decide if the deep tarsal vessels could be seen, time that a clinical examiner often does not have under field conditions. It is unlikely to be the result of altered magnification in the photograph slides, because these were set to be 1:1 magnification. Eyes in the clinical examination and in the slides were both read with identical magnification, 2·5× loupes.

Photographic data for a total of 4% (five subjects) in this series were lost because of bilateral ungradable photographs. Thirteen other subjects had photographs which were ungradable, but for one eye only. Data from the clinical grading showed agreement in the trachoma profile between the right and left eyes was 91%. Therefore either eye could represent the trachoma status for these individuals. This small loss (4%) does need to be factored in planning the size of a trachoma study. In order to minimise loss of data both eyes probably should be photographed for field studies.

In summary, photographic documentation of trachoma appears to be a valid and reproducible technique that may be of value for the assessment of change in trachoma over time.

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# Histopathological findings in the iris of dapsone treated leprosy patients

F Brandt, H M Zhou, Z R Shi, N Rai, L Thuladar, H Pradhan

## Abstract

**From 43 Nepalese leprosy patients skin smear negative, and treated with dapsone (diamino diphenyl sulphone), and without any sign of active leprosy or iritis, specimens from iridectomy during cataract surgery were studied histopathologically. Of 49 iris specimens only six (12%) were found to be without any histopathological change. Atrophy of the iris stroma was seen in 63% and neovascularisation in 6% of all cases. In 16% in which the dilator muscle could be detected, it was atrophic, and in 11% the pigmented epithelium was thinned and atrophic. Cellular inflammatory infiltrations were seen in 88% of all specimens. They were mostly slight in eyes which before operation had been without posterior synechiae of the iris. In most of the eyes in which posterior synechiae had been present moderate or heavy inflammatory cell infiltrates composed of lymphocytes and plasma cells, often associated with macrophages, neutrophils, or eosinophils, were found. In five iris specimens acid fast bacilli were present. This raises the question whether these can survive systemically despite dapsone chemotherapy in the iris, thus leading to dapsone-resistant leprosy and to recurrent iritis.**

Iritis is an important complication in patients with leprosy[1] and also in animals infected with *Mycobacterium leprae*.[2 3] The inflammation of the iris leads to posterior synechiae, atrophy of the iris,[4] decreased intraocular pressure,[5] and impairment of sight.[6]

The iritis in leprosy may be caused directly by the presence of the *M. leprae* in the iris or by a reaction to some antigenic substances of the bacilli or to antigen-antibody complexes, even when there is no intact or fragmented bacillus in the iris. An autoimmune type of reaction has also been suggested. The persistent and recurrent inflammation in the iris long after the systemic infection has been treated and the patient's disease has been brought under control is generally well known.

The presence of viable *M. leprae*, an acid fast bacilli (AFB) in the iris, with persistent and recurrent inflammations has been suggested, but till now without any definite proof. Whether living AFB remain in the eyeball after the lesions of the skin have been cured and the skin smear has become negative, and whether the recurrent iritis is the result of persistence or increase of these bacteria intraocularly, are questions that need elucidation.

The purpose of this study was to examine histologically iris specimens taken from dapsone treated, skin-smear negative, inactive leprosy patients from Nepal to look for histopathological changes and to search for AFB.

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## Material and methods

The clinical data were gathered from 43 Nepalese patients with leprosy. They included age, sex, duration of disease, type of leprosy, and findings in the anterior segment (lagophthalmus, corneal opacity, and posterior synechiae). The disease itself was classified according to the system of Ridley and Jopling[7] as modified by Leiker.[8] Tuberculosis was not diagnosed in any patient. All had received dapsone for many years and had become clinically inactive. From 49 eyes the iridectomy specimen was taken during cataract extraction. All specimens were fixed in 5% formalin and embedded in paraffin, and cut sections were stained with haematoxylin and eosin (H and E), periodic acid Schiff (PAS), modified Fite Faraco (after depigmentation), Gram, Giemsa, reticulum, and amyloid stains. The severity of the atrophic changes and the amount of inflammatory cell infiltrates in the iris, as well as the grade of the existing AFB, were classified in three grades: slight (+), moderate (++), and heavy (+++). The existence of AFB was determined and noted in the preparation. As a control group for analysis another 33 iridectomy specimens were taken from non-leprosy Nepalese patients of comparable age and sex.

## Results

### CLINICAL FINDINGS

Most of the patients were over 40, had suffered from leprosy for more than 20 years, and were borderline in type. Lagophthalmus was found in 29%, corneal opacity in 47%, and posterior synechiae in 57% of all the patients (Table I).

### HISTOPATHOLOGICAL FINDINGS

There was mild to severe atrophy of the iris stroma in 31 cases (63%). The branches of the stroma chromatophore cells were either shortened or had disappeared (Fig 1). In the most severe cases fibrotic tissue was increased and the number of blood vessels decreased. In some cases the stroma had completely turned into a mass of fibrotic tissue. But in many the atrophic change was not seen throughout the specimen. In one case the fibrotic tissue formed in the iris extended backwards and outwards, merging with the fibrotic membrane formed behind the posterior surface of the iris (Fig 2).

In five cases (10%) an increased number of blood vessels was seen in the stroma, while in

TABLE I *Clinical data and histological findings in iris specimens taken from dapsone treated leprosy patients during cataract surgery*

| | | | | | | | | *Histological findings* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | *Stroma* | | | | | | | | | | | |
| *Patient data* | | | | | *Findings in anterior eye segment* | | | | | *Cell infiltrations* | | | | | | | | | |
| *Patient* | *Sex* | *Age (years)* | *Duration of disease (years)* | *Type of leprosy* | *Lagophthalmos* | *Corneal opacity* | *Posterior synechiae* | *Atrophy* | *Blood vessel* | *Lymphocyte* | *Plasma cell* | *Macrophage* | *Neutrophils* | *Eosinophils* | *Sphincter atrophy* | *Dilator atrophy* | *Pigment epithelium atrophy* | *Anterior surface* | *Acid fast bacilli* |
| 1 | F | 60 | 8 | T | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 2 | M | 56 | 14 | T | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – |
| 3 | F | 70 | 25 | BT | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 4 | F | 70 | 22 | BT | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – |
| 5 | F | 63 | 22 | BT | – | – | – | – | – | + | + | – | – | – | * | – | – | – | – |
| 6 | F | 50 | 22 | BT | – | – | – | – | D | + | + | – | – | – | * | – | – | – | – |
| 7 | F | 55 | 28 | BT | – | – | – | +++ | D | – | – | – | – | – | + | + | – | – | – |
| 8 | F | 60 | 30 | BT | + | – | – | + | – | + | + | – | – | – | – | – | – | – | – |
| 9 | F | 80 | 72 | BT | + | – | – | – | D | + | – | – | + | + | – | – | – | – | – |
| 10 | M | 60 | 19 | BT | – | + | + | – | – | ++ | ++ | + | + | – | – | – | – | – | – |
| 11 | M | 46 | 20 | BT | – | + | + | + | – | – | – | – | – | – | * | – | – | – | – |
| 12 | M | 60 | 19 | BT | – | + | + | + | – | + | + | – | – | – | * | – | – | – | – |
| 13 | F | 59 | 18 | BT | – | + | + | +++ | D | – | – | – | – | – | – | + | – | – | – |
| 14 | F | 54 | 42 | BT | + | + | + | – | – | + | + | – | + | – | – | – | – | – | – |
| 15 | M | 35 | 26 | BT | + | + | + | – | I | +++ | +++ | + | – | – | * | – | – | N | – |
| 16 | M | 75 | 40 | BT | + | + | + | – | – | – | – | – | – | – | * | * | * | N | – |
| 17 | M | 37 | 26 | BT | + | + | + | + | – | ++ | +++ | + | + | – | * | – | – | N | – |
| 18 | M | 65 | 19 | BT | + | + | + | + | – | +++ | ++ | + | + | + | – | * | * | E | – |
| 19 | M | 58 | 41 | BT | + | + | + | ++ | – | ++ | ++ | + | – | – | – | – | – | – | – |
| 20 | M | 60 | 10 | BB | – | + | – | + | – | – | – | – | – | – | – | – | – | – | – |
| 21 | M | 28 | 22 | BL | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 22 | M | 65 | 12 | BL | – | – | – | – | – | – | + | – | – | – | * | – | – | – | – |
| 23 | F | 71 | 35 | BL | – | – | – | – | – | + | ++ | + | + | – | * | – | * | – | – |
| 24 | F | 65 | 40 | BL | – | – | – | + | – | + | – | – | – | – | – | – | – | – | – |
| 25 | M | 60 | 23 | BL | – | – | – | ++ | – | – | – | – | – | – | – | – | – | – | – |
| 26 | F | 47 | 41 | BL | – | – | + | + | – | + | ++ | + | + | – | * | – | – | – | – |
| 27 | M | 52 | 24 | DL | – | | + | + | I | + | + | + | – | – | * | * | * | – | – |
| 28 | M | 60 | 6 | BL | + | – | + | + | – | + | – | – | – | – | * | – | – | – | – |
| 29 | F | 50 | 28 | BL | + | – | + | + | I | + | + | + | + | – | * | – | – | – | + |
| 30 | M | 34 | 22 | BL | – | + | + | – | – | + | ++ | – | + | – | – | – | – | – | – |
| 31 | M | 46 | 40 | BL | – | + | + | – | – | + | ++ | – | + | + | * | – | – | – | + |
| 32 | M | 34 | 22 | BL | – | + | + | + | – | + | + | – | – | – | * | – | – | – | – |
| 33 | M | 50 | 16 | BL | – | + | + | + | – | ++ | + | + | + | – | * | – | – | – | + |
| 34 | M | 46 | 40 | BL | – | + | + | ++ | D | + | ++ | ++ | + | – | – | + | + | – | – |
| 35 | M | 26 | 19 | BL | + | + | + | + | – | + | ++ | + | + | + | * | – | – | – | – |
| 36 | M | 52 | 34 | BL | + | + | + | + | I | + | ++ | – | + | – | * | – | – | – | – |
| 37 | M | 60 | 39 | BL | + | + | + | + | D | + | – | – | + | – | * | + | + | – | – |
| 38 | M | 60 | 38 | BL | + | + | + | ++ | D | + | + | – | – | – | * | + | + | – | – |
| 39 | M | 60 | 20 | LL | – | – | – | – | – | – | – | – | – | – | * | * | * | – | – |
| 40 | F | 72 | 40 | LL | – | – | – | – | – | + | – | – | – | – | * | – | * | – | – |
| 41 | F | 50 | 35 | LL | – | – | – | + | – | + | ++ | – | – | – | * | – | – | E | – |
| 42 | F | 80 | 26 | LL | – | – | – | ++ | – | + | + | + | + | – | – | – | – | – | + |
| 43 | F | 59 | 40 | LL | – | + | – | + | – | + | – | – | – | – | * | * | * | – | – |
| 44 | M | 72 | 40 | LL | – | – | – | – | – | + | – | – | – | – | * | – | * | – | – |
| 45 | M | 48 | 20 | LL | – | – | + | – | – | – | – | – | – | – | * | – | – | – | – |
| 46 | F | 50 | 20 | LL | – | – | + | + | – | + | – | – | + | – | * | – | – | – | – |
| 47 | M | 60 | 40 | LL | – | – | + | + | D | + | ++ | + | + | – | * | – | – | – | + |
| 48 | M | 56 | 17 | LL | – | + | + | + | I | + | + | – | + | – | * | – | – | – | – |
| 49 | F | 63 | 26 | LL | – | + | + | ++ | – | + | ++ | – | + | – | – | + | + | F | – |

T=Tuberculoid. BT=Tuberculoid-borderline. BB=Borderline-borderline. BL=Borderline-lepromatous. LL=lepromatous. *The tissue was not found or recognised in the specimen. D=decreased, E=exudation at the anterior surface of the iris. F=fibrous membrane formed behind the posterior surface of the iris. I=increased. N=neovascularisation.

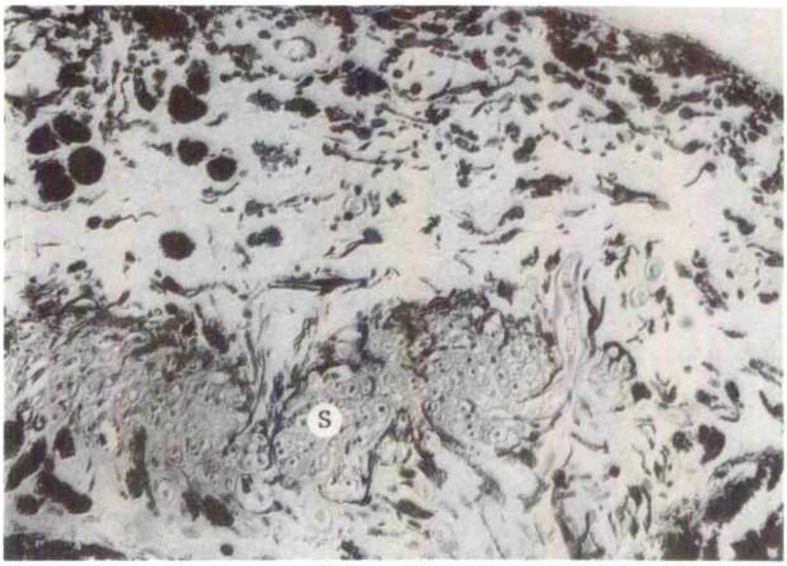


*Figure 1: Branches of many stroma cells decreased in number or vanished. The inflammatory cell infiltration is slight. The sphincter muscle (S) seems to be intact. (H and E, ×332.)*

eight cases (16%) the number was decreased. In 36 cases (73%) there were various amounts of lymphocytes and plasma cells in the stroma, sometimes accompanied by macrophages, neutrophils, and eosinophils (Figs 3, 4) and large Russell's bodies (Fig 5), of which the diameter sometimes exceeded up to 40 micra among the plasma cells. Cellular exudates were attached to the anterior surface of the iris in two cases (4%), and in three cases (6%) proliferated capillaries were protruding from the anterior surface (Fig 6).

The dilator muscles were atrophic (Fig 7) in six of those 44 cases in which the muscle was seen (14%). The pigment epithelium was seen in 41 cases, and was thinned and atrophic in four cases (10%).

In three iris specimens one or several bacilli were seen in the stroma cells or in the stroma itself. In a fourth case several bacilli were found in the wall of a blood vessel (Fig 8), and in the fifth specimen large amounts of AFB were found throughout the entire iris (Fig 9), mostly within the stroma and the infiltrating cells (Table I).

In one-third of the cases (11/33) in the control group of patients without leprosy the branches of the melanin-containing stroma cells were shortened. The iris showed no atrophy. In four cases there were lymphocytes, plasma cells, and neutrophil infiltrations, but all in slight degree. No AFB was found.

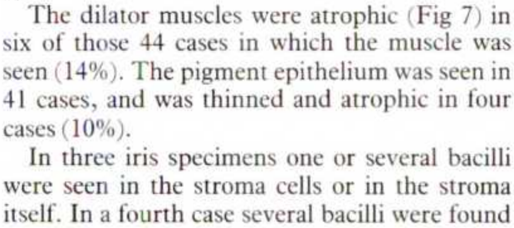


*Figure 2: The fibrous tissue in the iris is increased. The adhesion to the lens capsule is obvious. The sphincter muscle (S) is infiltrated by some cells. (H and E, ×60.)*

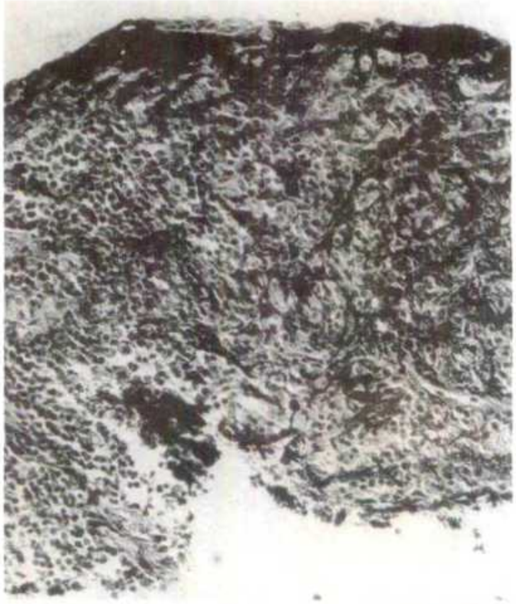


*Figure 3: Large amount of inflammatory cells infiltrate the stroma of iris. (H and E, ×78.)*

## Discussion

In the eyes of Nepalese leprosy patients posterior synechiae are often seen in 'advanced cases' in the leprosarium,[9,10] and less often but not rarely, in outpatients examined in the leprosy clinics.[11,12] Often not only had posterior synechiae developed after iritis but also complicated cataract and blindness had done so.[13,14] All the 49 iris specimens were obtained during cataract surgery from leprous patients who were found to be negative to a skin smear test and when there were no clinical signs of active iritis. Histological studies of the iris specimens showed no correlation between the severity of histological changes in the tissue and the duration of disease in each individual, nor in the differences in age or sex of the patients.

A significant difference could be seen in the tissue histology between those showing only lagophthalmus/corneal opacity and those having signs of previous iritis, and posterior synechiae in particular. Whereas in the former only slight histological changes were seen for the most part, the latter mostly showed moderate to heavy signs of inflammation. Lymphocytes, mast cells, and even Russell's bodies were frequently seen. The Russell's bodies were larger in our specimens than those usually found in other inflammatory conditions. The presence of macrophages and neutrophils was practically restricted to specimens obtained from eyes having posterior synechiae preoperatively. It is likely that postoperative iritis may recur in those leprosy patients following cataract extraction, and these eyes should therefore be watched most carefully.[15,16]

The atrophy of dilator muscles of the iris that was seen in the specimens may be due to neuroparalysis as a sequel to the chronic and recurrent inflammatory processes in leprous patients. The early atrophic changes in the iris dilator muscles may not be easily discovered under the light microscope, especially when the bleaching of the melanin granules in the tissue has not been complete.

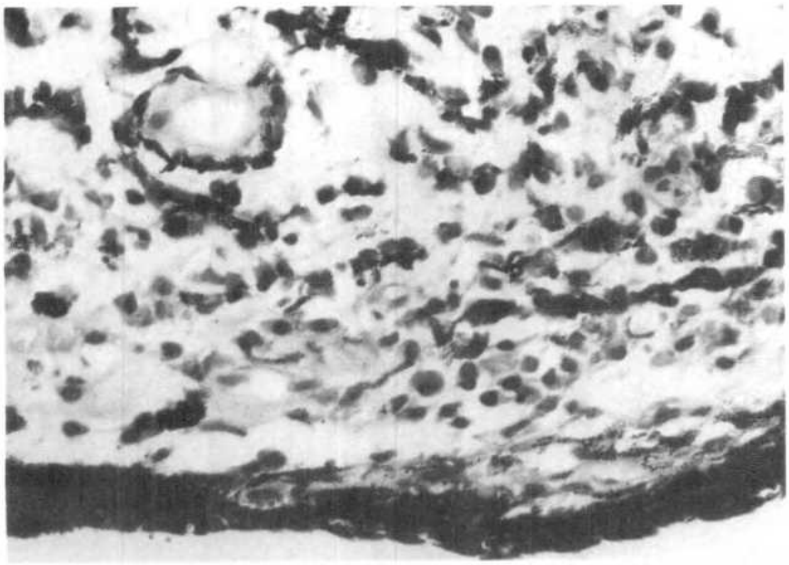


*Figure 4: Lymphocytes, plasma cells, and macrophages infiltrate the matrix of the iris. (H and E, ×817.)*

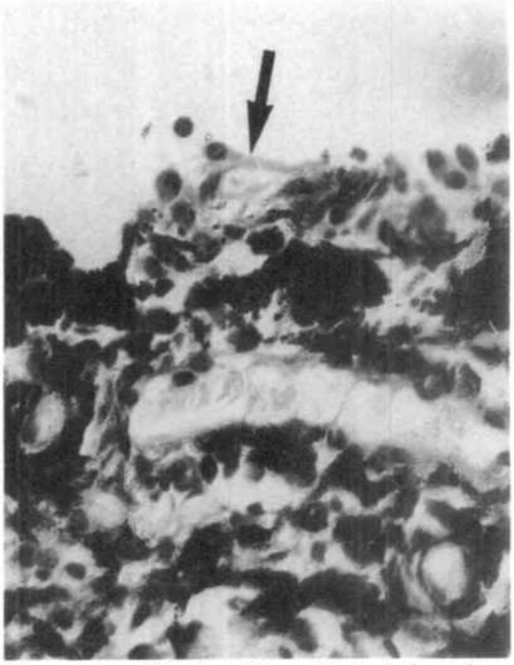


*Figure 6: A small blood vessel (arrow) protrudes forwards from the anterior surface of the iris; neovascularisation of iris. (H and E, ×1000.)*

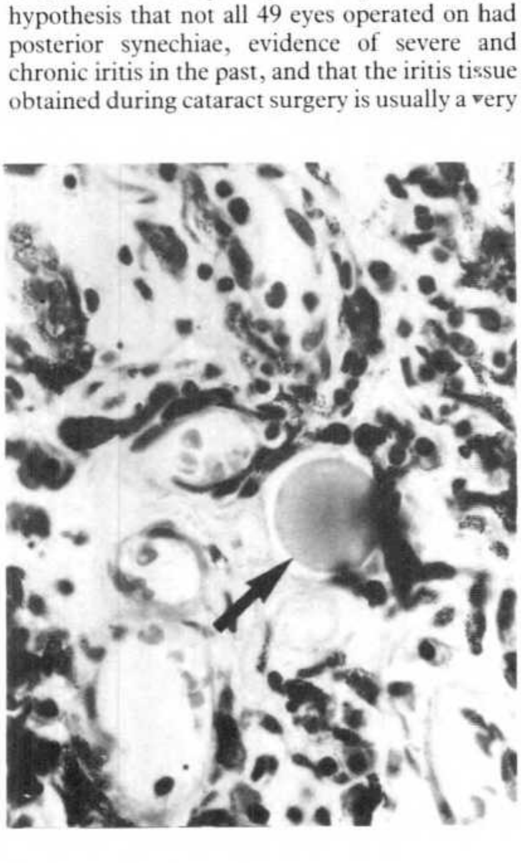
The neovascularisation observed on the anterior surface of the iris could be due to chronic inflammation, as also the fibrous membrane formed behind the iris.

Amyloid deposits were not detected in any of our specimens. The five specimens of iris in which the presence of AFB was revealed were from lepromatous patients who were, with one exception, found to have posterior synechiae preoperatively. These AFB-containing specimens also showed slight, moderate, or heavy cellular infiltrations with lymphocytes, mast cells mostly associated with macrophages, neutrophils and eosinophils. The histology seen in our specimens is not of a granuloma but of a non-granulomatous inflammation. The fact that only five specimens out of 49 (10%) were found to have AFB can perhaps be explained by the hypothesis that not all 49 eyes operated on had posterior synechiae, evidence of severe and chronic iritis in the past, and that the iritis tissue obtained during cataract surgery is usually a very small specimen. Consequently the specimen obtained may have just missed the AFB lying in the tissue.

Like others who have found AFB in different tissues, as in nerve[17] or skin[18] of dapsone treated leprous patients, we cannot say whether the AFB detected in the five specimens of iris tissue were viable or not at the time of surgery. But if the bacilli were surviving at the time of their removal from a living eye in patients showing an inactive state of the disease following years of treatment with dapsone, it can be conjectured that either the dapsone has a poor intraocular penetration or the bacilli have developed resistance to the drug. Thus it remains a matter of great concern if the systemic relapse of dapsone treated and apparently cured leprous patients is due to the dissemination of surviving and probably dapsone resistant AFB from within the eye.

It has been seen that iritis occurs many years after clinical inactivation of the disease by treatment in some patients. This iritis may perhaps be the first sign of a systemic relapse of the disease after long quiescence.[19] But, even if the AFB had become inactive or fragmented, iritis might also occur or recur when the antigen undergoes any reaction with antibodies, resulting in the clinical picture of iritis.

*Figure 5: Russell's body (arrow) among the infiltrated inflammatory cells in the iris. (H and E, ×400.)*



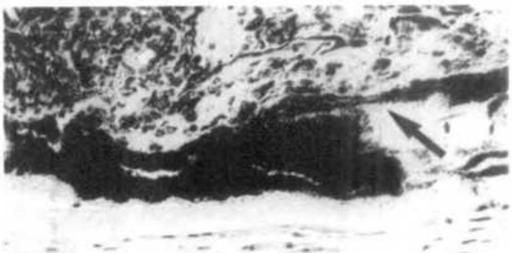


*Figure 7: The pigment epithelium is atrophic (arrow) and the dilator muscle is beyond recognition. In front of the adherent lens capsule the formed fibrous membrane is distinct. (H and E, ×285.)*

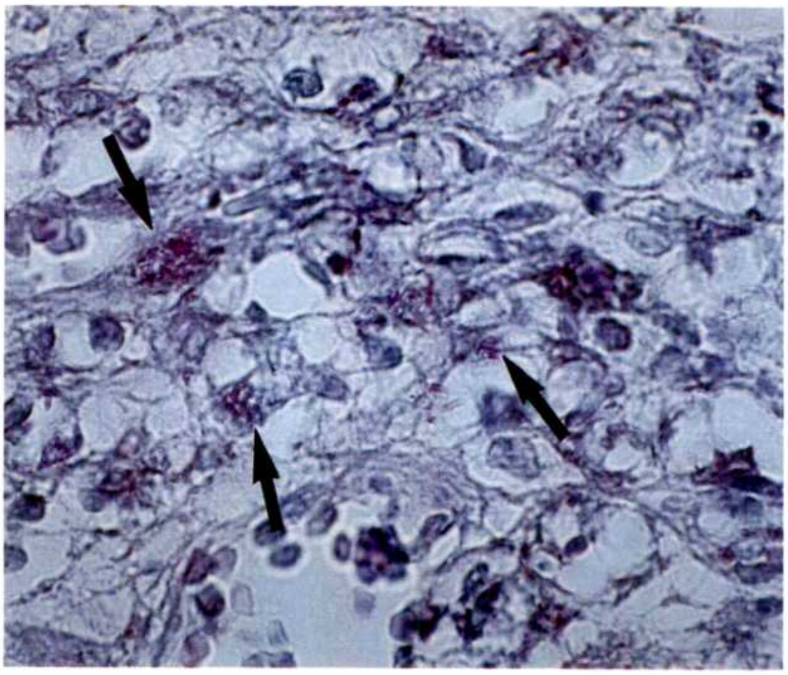


*Figure 8: Several acid fast bacilli (arrows) in the wall of a blood vessel. (FF, × 1000.)*

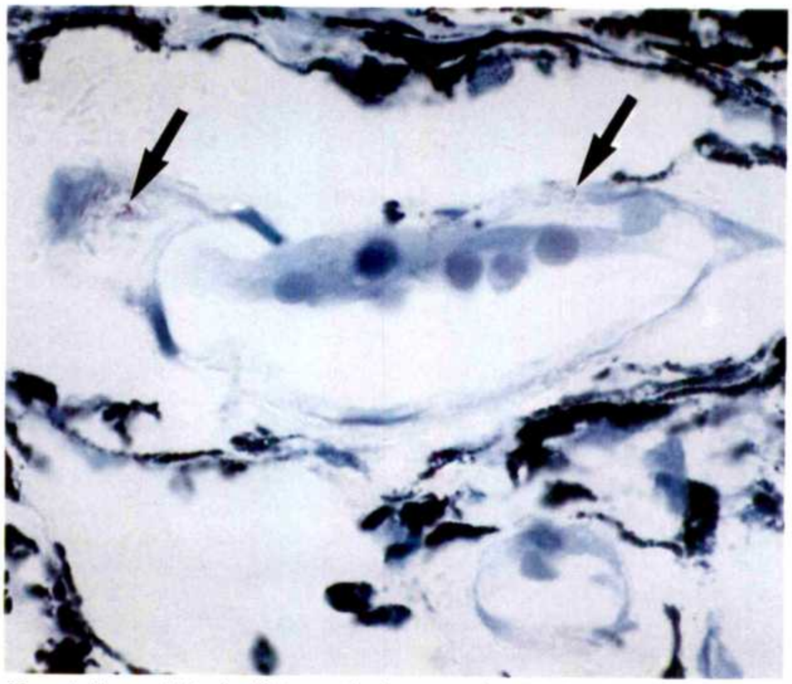


*Figure 9: Many acid fast bacilli (arrows) in the stroma cells. (FF after depigmentation, × 1000.)*

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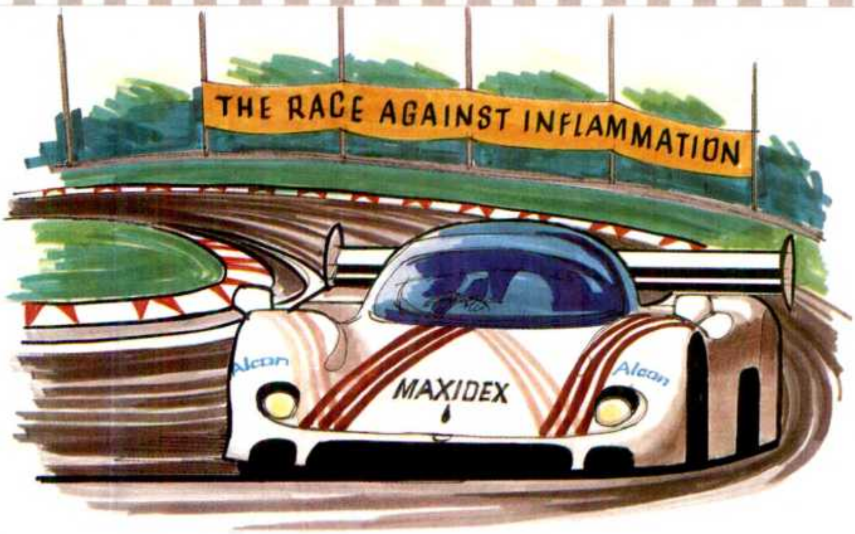

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British Journal of Ophthalmology, 1990, 74: 19–21

# Topical use of indomethacin on the day of cataract surgery

A E T Searle, J L Pearce, D E Shaw

**Abstract**

**The use of topical indomethacin in the prevention of surgically induced miosis has been documented.[1 2] However, in these previous prospective trials this prostaglandin synthetase inhibitor was administered the day before surgery. With the frequency of 'day case' cataract surgery increasing, an efficient preoperative mydriatic regimen is important. In this study we considered the use of topical indomethacin as an addition to a regimen already implemented. One hundred and fourteen eyes underwent intercapsular cataract surgery, of which 64 were randomised to receive topical aqueous indomethacin one hour beforehand, and 50 eyes, which did not receive indomethacin formed the comparison group. Topical indomethacin reduced the miosis which occurs during cataract surgery whether performed under local or general anaesthesia. The operating time was shorter for eyes with less surgically induced miosis.**

Mydriasis achieved preoperatively, before inter- or endocapsular cataract surgery, may influence the length of each surgical procedure and the complications encountered. Topical indomethacin has been shown to maintain pupil dilatation during cataract surgery,[1 2] but in each study this prostaglandin synthetase inhibitor was administered on the evening before surgery. It is not always practicable to administer eye drops on the day before surgery, and mydriatic regimens may start only 1–2 hours preoperatively. The desired effect of indomethacin in such circumstances is unproved.

In this study the effect on perioperative pupil size of administering topical indomethacin one hour before cataract surgery was investigated.

## Patients and methods

Ninety two patients undergoing intercapsular cataract surgery by one surgeon (JLP), at the Alexandra Hospital, Redditch, between 2 November 1987 and March 1988 were included: 22 patients underwent bilateral surgery and 70 unilateral surgery. The patients' ages ranged from 14 to 95 years (mean 71·16 years). A total of 114 eyes were observed.

All patients falling into one of the following groups were excluded: diabetes mellitus; receiving systemic drugs with autonomic effects; past history of glaucoma, uveitis, or herpes zoster ophthalmicus; previous intraocular surgery; previous history of trauma to the eyes, face, or head; and abnormal pupillary responses to light stimulation.

Patients were randomly allocated to a group receiving preoperative topical indomethacin – that is, to a treatment group or to a non-treatment group – by the first author. In cases of bilateral surgery both eyes were allocated to the same group.

### MYDRIATIC REGIMEN

One hour preoperatively *all* eyes received the following topical mydriatic treatment, administered by the nursing staff on the ward: 1 drop of cyclopentolate 1% and phenylephrine 10% every 15 minutes for 45 minutes before surgery.

Eyes allocated to the treatment group also received: 1 drop of aqueous indomethacin 1% (supplied by Merck Sharp and Dohme on a named patient basis) every 15 minutes for 45 minutes before surgery. Permission to use this drug was obtained from the local ethical committee.

### ANAESTHESIA

Thirty eyes underwent cataract surgery with local anaesthesia (LA alone). Eighty four eyes underwent cataract surgery with a combination of local and general anaesthesia (LA plus GA). All patients undergoing LA alone received one hour before surgery a peribulbar injection of 4 ml of a 50:50 mixture of 4% plain lignocaine and 0·75% bupivacaine to attain ocular anaesthesia and akinaesia and 4 ml of the same mixture as a facial injection by Van Lindt's method to attain orbicularis oculi akinaesia.

All patients undergoing LA plus GA received a peribulbar injection of 0·75% bupivacaine at the induction of general anaesthesia within five minutes of surgery.

### CATARACT SURGERY

Each intercapsular cataract extraction was performed by JLP. Information on the allocation of each eye to a treatment or non-treatment group was not made available to the surgeon preoperatively.

The operating technique, which did not alter during the four-month period, included: (*a*) measurement of the horizontal diameter of the pupil to 0·5 mm with a caliper under view with the operating microscope, after insertion of the superior rectus suture, by the surgeon; (*b*) a corneoscleral wound; (*c*) anterior capsulotomy after injection of sodium hyaluronate; (*d*) an intercapsular technique of irrigation and aspiration of cortical lens matter; (*e*) insertion of an intraocular posterior chamber lens into the capsular bag and positioning with a Sinskey hook; (*f*) anterior capsulectomy under sodium hyaluronate.

During the cataract surgery a balanced salt solution containing 0·3 ml of 1:1000 adrenaline

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in 250 ml was used to wet the cornea and as an intraocular infusion.

All eyes developing interoperative complications were excluded.

### OPERATING TIME

The time elapsing between both pupil measurements was recorded to the nearest second with a stop clock in the theatre.

Sixty-four eyes were included in the treatment group, of which 50 underwent cataract surgery with combined LA plus GA and 14 underwent cataract surgery with LA alone. Fifty eyes were included in the non-treatment group, of which 34 eyes underwent cataract surgery with combined LA plus GA and 16 eyes underwent cataract surgery with LA alone. Comparison of the initial and continual mydriatic effect was made between the treatment and non-treatment groups of eyes, and means and standard deviations are given. As common statistical methods cannot be used when the outcome variable is not independent, and eyes within a person are unlikely to be independent, the method of Rosner[3] was employed in which a correction for this intrasubject correlation is made. One patient treated on one side only, aged 14 years, the youngest, was excluded from the analysis, as his operation time (35 minutes) was 10 SDs away from the mean. The youngest subject in the study after completion of the study was 27 years old.

## Results

The mean preoperative pupil diameter of all 113 studied eyes was 8·2 mm (SD 1·1), and the mean reduction after surgery was 1·5 mm (SD 1·0) (the proportionate change being 0·19 (SD 0·12)). The mean operation time was 15·6 min (SD 1·9).

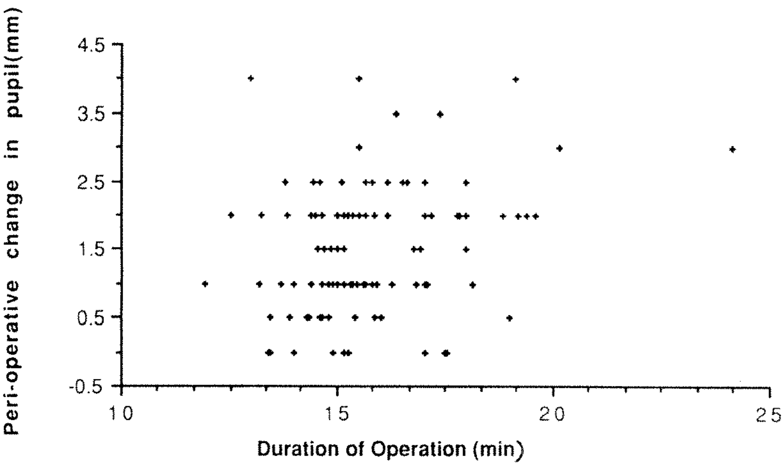
The preoperative pupil diameters were inversely related to the age of the patient, this relationship being only marginally significant ($p=0·1$) but were larger in the LA+GA group (8·3, SD 0·9) than in the LA alone group (7·8, SD 1·3, $p=0·044$). The initial pupil diameters were not significantly different between the treatment and non-treatment groups.

TABLE I *Initial and changes in pupil diameter by treatment and anaesthetic groups*

| | *Pupil diameters in mm: mean (SD), number* | |
|---|---|---|
| | *Treatment* | *Non-treatment* |
| Initial pupil diameter | 8·1 (1·1) n=63 | 8·3 (1·0) n=50 |
| Difference from preoperative pupil diameter | | |
| LA+GA | 1·2 (0·9) n=49 | 1·8 (0·8) n=34 |
| LA alone | 1·3 (1·0) n=14 | 1·9 (1·2) n=16 |
| Total | 1·2 (0·9) n=63 | 1·8 (0·9) n=50 |
| Proportionate change from preoperative pupil diameter | | |
| LA+GA | 0·15 (0·11) n=49 | 0·21 (0·09) n=34 |
| LA alone | 0·17 (0·13) n=14 | 0·25 (0·17) n=16 |
| Total | 0·16 (0·11) n=63 | 0·22 (0·12) n=50 |

The change in pupil diameter during surgery was inversely related to the duration of surgery ($p<0·001$) (Fig 1) and to the treatment group ($p<0·001$) (Table I). These effects were independently significant. The non-administration of indomethacin resulted in a larger perioperative reduction in pupil diameter. The age of the patient and the type of anaesthetic used were not significantly related to the reduction in pupil size. The mean reductions in pupil diameter in the two treatment groups are shown in Table I. Also in Table I are the mean changes in pupil diameters for each of the treatment groups subdivided by each of the anaesthetic groups. The treatment effect was the same for each of the anaesthetic groups. The numbers of eyes in each of the treatment and non-treatment groups that had at least 2·0 mm perioperative miosis were 20 (31·7%) and 30 (60·0%) respectively. The operating times for the two groups were identical and were 15·6, SD 1·9 ($n=63$) and 15·6, SD 1·9 ($n=50$) minutes respectively.

*Figure 1: Change in pupil diameter by length of operation.*



## Discussion

For efficient cataract surgery maintained mydriasis is necessary. We have shown that for one surgeon increased change in pupil diameter is associated with longer surgical procedures. By using topical aqueous indomethacin the amount of surgical miosis was reduced. Less than a ⅓ (31·7%) of eyes underwent more than 2·0 mm of miosis compared with almost ⅔ in the non-treatment group (60·0%). This prevention of miosis was found in eyes of patients undergoing LA alone and LA plus GA. However, overall initial pupil diameters were greater for the LA and GA group. The anaesthetists in this unit did not use any premedication in patients over the age of 65 (25/113 eyes) in this study and did not use atropine as a premedication in the patients under the age of 65. Droperidol, which was used in some of the younger patients as a premedication, may have a mild atropine effect.[4] Apart from this tentative suggestion, the significant difference in the initial pupil size between the use of combined general and local anaesthesia and local anaesthesia alone in this centre is unexplained.

In view of the results of this study it is suggested that the minimum aqueous level of idomethacin needed to prevent surgical miosis may be obtained by administration less than 24 hours preoperatively. The use of topical indomethacin one hour preoperatively reduced surgical miosis and may be of practical benefit in both day case and inpatient cataract surgery.

We thank Ann Badger, secretary to Mr Pearce, for administrative help; Allan Davies, Assistant Regional Information Manager, West Midlands Regional Health Authority, and Lucy Titcomb, pharmacist in charge, the Birmingham and Midland Eye Hospital, for pharmacological advice.

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# Pseudophakic accommodation? A study of the stability of capsular bag supported, one piece, rigid tripod, or soft flexible implants

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**Abstract**

**A group of pseudophakic patients was investigated to determine whether their implants shift along an anteroposterior axis under different conditions of ciliary muscle stimulation. There was no statistically significant change in refraction after either pilocarpine or cyclopentolate administration. A change in anterior chamber depth between the position after pilocarpine and that after cyclopentolate was found. It appears that rigid posterior chamber implants do move backwards on ciliary muscle relaxation, but by a maximum 0.25 mm. This is not thought to represent a mechanical threat to ocular health. It is also not enough to account for the apparent accommodative ability of some pseudophakic patients. The possible causes for this phenomenon are discussed.**

Recent research in cataract surgery has demonstrated the concept of using an elastic polymer injected into the capsular bag to provide an implant which can accommodate.[1,2] In addition multifocal implant lenses are being developed for widespread use. It is already known that some pseudophakic patients fitted with conventional implants may have good near and distance vision using their distance correction only. This phenomenon has been termed 'apparent accommodation' and is ascribed to a number of different optical properties of the eye/implant lens system.[3] An alternative explanation for this observation is that the implant lens may shift relatively to the nodal point of the eye along the anteroposterior axis (z axis) during an effort to accommodate, particularly when the lens is placed entirely within the capsular bag. If correct, such movement might represent optical convenience. However, the required lens movement could also pose a threat to ocular health through lens displacement, pupil distortion, and iris chafe, thereby negating many of the advantages of the posterior chamber lens.

In this study a group of patients was assessed for intraocular lens (IOL) position and objective refraction under various conditions of ciliary muscle stimulation. All 29 pseudophakic eyes had either one-piece tripod rigid PMMA lens (Haworth Equilimb type, Rayner Co. Ltd, UK) or a lens made of flexible PolyHEMA (Iogel type, Alcon Ltd, UK). ALL these lenses were placed within the capsular bag at surgery. The object of this examination was to determine whether either type of lens moves with the eye, thereby causing a change in refractive power.

## Materials and methods

A group of 17 patients was examined, comprising nine males and 8 females, aged 35–72 with mean age 68. All had undergone cataract surgery with IOL implantation performed by a single surgeon within the preceding five years. Twenty one eyes were fitted with rigid tripod PMMA lenses and eight had soft flexible PolyHEMA lenses. Four patients were monocular pseudophakics, and one had one eye.

Each patient had retinoscopy and refraction measured and the optimal distance and near vision recorded; all measurements were made by a single observer. Anterior chamber (AC) depths were then estimated with the Haag-Streit slit-lamp pachymeter using the recommended +6·00 D overcorrection in the observer eyepiece.[4] Depths were measured from the corneal endothelial surface to the anterior surface of the

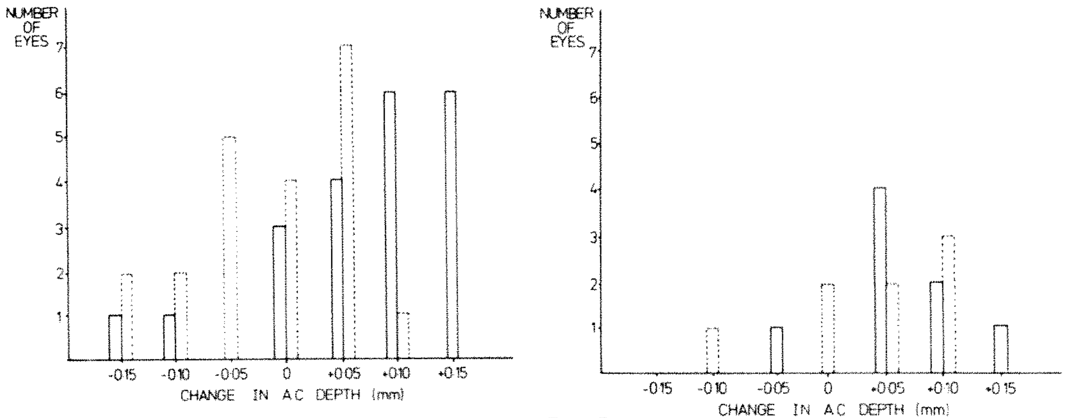

*Fig. 1A*

*Fig. 1B*

*Figure 1: Change in anterior chamber depth from baseline after either cyclopentolate (——) or pilocarpine (– – – –). 1A shows the results for rigid lenses. 1B shows the results for flexible lenses.*

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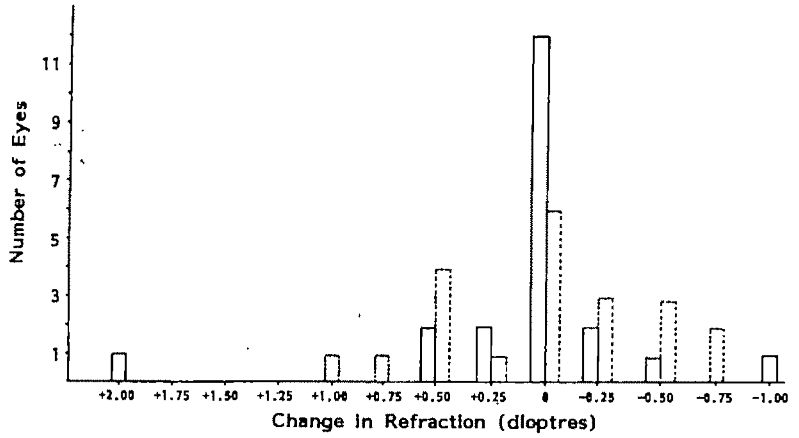

*Fig. 2A*

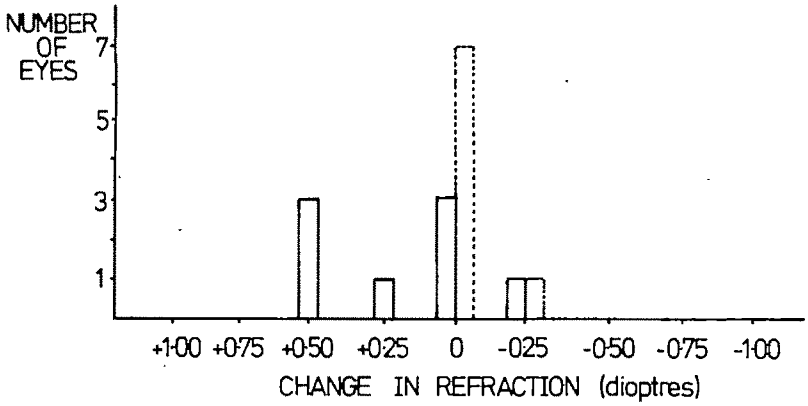

*Fig. 2B*

*Figure 2: Change in refraction from baseline after either cyclopentolate (——) or pilocarpine (– – – –).*
*2A shows the results for rigid lenses.*
*2B shows the results for flexible lenses.*

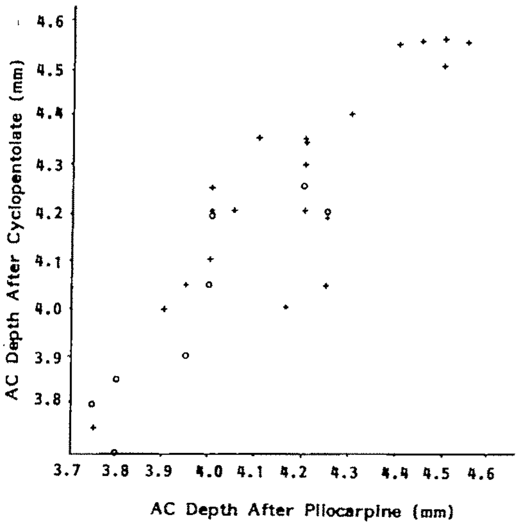

*Figure 3: Anterior chamber depth after cyclopentolate compared with anterior chamber depth after pilocarpine for each eye.*
*Rigid lenses are shown as +.*
*Flexible lenses are shown as o.*

IOL on the optic axis. On all occasions three successive estimates were made and then averaged with no access to the previously recorded refraction.

These measurements of refraction and AC depth were made on four separate occasions. Firstly, a base-line set of measurements was made. The examination was repeated following the instillation of 2% pilocarpine three times a day for two days to provide ciliary muscle stimulation. One week later the measurements were repeated following the instillation of cyclopentolate at 15-minute intervals for 45 minutes to relax the ciliary muscle. Finally, to provide an estimate of observer reliability, the measurements of refraction and AC depth, after cyclopentolate administration were repeated after a further seven days and the results compared with those obtained the preceding week.

On all occasions measurements were made without reference to any previously determined values of refraction and AC depth. All values were derived with the patient sitting with head vertical and eyes level to eliminate any possible effect of gravity on the antero-posterior lens position.

## Results

In Figure 1 the change in AC depth after pilocarpine and then cyclopentolate instillation into pseudophakic eyes is shown by comparison with the base-line measure. Figure 1A shows the numbers of patients with rigid lenses, while Figure 1B displays the equivalent results for flexible implants. (The average value for baseline AC depth was found to be 4.35 mm for rigid lenses and 4.05 mm for flexible implants.)

Figure 2 shows the changes in refractive error after pilocarpine or cyclopentolate compared with the baseline measurement. Figure 2A demonstrates the results for rigid lenses and Figure 2B the results for flexible implants. The only consistent shift in any measurement seems to be a deepening of the anterior chamber of those eyes with rigid tripod implants after cyclopentolate administration, as seen in Figure 1A.

Figure 3 combines the information from Figures 1 and 2 to demonstrate the maximal change in AC depth by comparing the AC depth values obtained after pilocarpine administration directly with those recorded after cyclopentolate. If there were no change in AC depth, all eyes would show results plotted on the 45° leading diagonal. Both rigid and flexible implants are shown in this graph.

A paired Student's *t* test showed that for rigid tripod lenses there is a significant difference between the AC depths with pilocarpine and cyclopentolate ($p=0.01$). Deeper anterior chambers were found with cyclopentolate than after pilocarpine, with a maximum recorded difference of 0·25 mm in the case of rigid lenses only. There was no significant difference between AC depths for flexible lenses ($p=>0{\cdot}2$).

Figure 4 compares the refractive error found after pilocarpine administration with that found after cyclopentolate. There was no significant difference in the refractive error in these two conditions for either type of implant ($p>0{\cdot}2$ by student's *t* test), as illustrated by the fact that the points are evenly scattered about the leading diagonal.

Table 1 shows details of 24 eyes for which full details of baseline visual capability were obtainable. The lens type and best corrected distance visual acuity are shown together with the refractive correction necessary to achieve that acuity. In the adjacent column the reading acuity achieved by the distance spectacle correction is shown. This column therefore gives some indication of the extent of apparent accom-

TABLE I *Near and distance vision of pseudophakic eyes using distance correction only*

| *Eye* | *Implant* | *Distance VA* | *Distance correction* | *Near VA* | *Distance for near VA (cm)* |
|---|---|---|---|---|---|
| 1 | Eq | 6/6 | −3·25 | N8 | 22 |
| 2 | Eq | 6/6 | −3·50/+0·50×90 | N14 | 23 |
| 3 | Eq | 6/9 | +4·50/+1·50×105 | N14 | 34 |
| 4 | Eq | 6/12 | 0/+1·50×175 | N14 | 38 |
| 5 | Eq | 6/5 | +1·00 | N12 | >50 |
| 6 | Iog | 6/5 | +1·25/+1·00×180 | N10 | 34 |
| 7 | Eq | 6/9 | 0/+1·50×165 | N14 | >50 |
| 8 | Iog | 6/6 | −0·50/+1·00×175 | N5 | 34 |
| 9 | Iog | 6/6 | +0·50/0·50×75 | N18 | 20 |
| 10 | Eq | 6/6 | −1·50+2.20×170 | N5 | 18 |
| 11 | Eq | 6/5 | −0·25/0·75×30 | N8 | 35 |
| 12 | Iog | 6/6 | −0·75/+2·00×90 | N10 | 32 |
| 13 | Iog | 6/6 | −1·25/+2·75×180 | N18 | 30 |
| 14 | Eq | 6/6 | 0/+3·50×170 | N18 | 38 |
| 15 | Eq | 6/9 | +1·00/+1·50×150 | N18 | 32 |
| 16 | Eq | 6/6 | +0·50/+2·00×175 | N18 | 28 |
| 17 | Eq | 6/6 | +0·50/+1·50×110 | N8 | 34 |
| 18 | Eq | 6/9 | +1·50/+0·50×90 | N18 | 50 |
| 19 | Eq | 6/6 | +0·50 | N12 | 25 |
| 20 | Eq | 6/6 | +0·25/+0·75×175 | N12 | 26 |
| 21 | Eq | 6/12 | +2·00/+2·00×60 | N24 | 20 |
| 22 | Iog | 6/6 | +2·25/+1·25×140 | N8 | 20 |
| 23 | Eq | 6/5 | +2·25/+2·00×15 | N12 | 18 |
| 24 | Eq | 6/5 | 0/+5·00×50 | N18 | 18 |

Eq=eyes with Haworth Equilimb type rigid lenses. Iog=eyes with soft flexible Iogel implants.

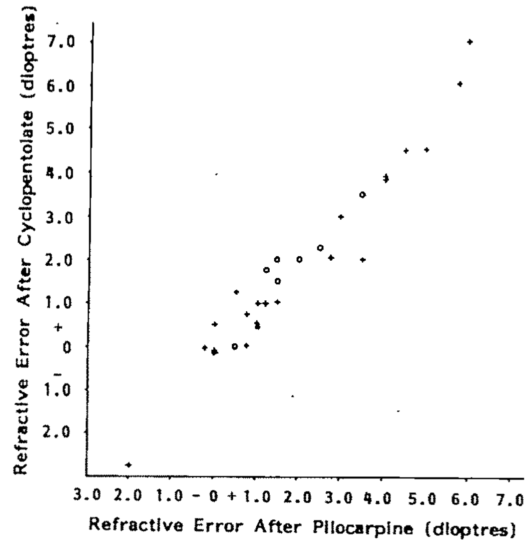

*Figure 4: Refraction after cyclopentolate compared with refraction after pilocarpine.*
*Rigid lenses are shown as +.*
*Flexible lenses are shown as o.*

modative ability in our patient group. The last column of the table shows the closest distance at which this reading acuity was obtained.

Figure 5A demonstrates the reproducibility of our methods of measurement by comparing the AC depths on two consecutive occasions. The correlation coefficient for these records was r=0·93 for rigid lenses and r=0.79 for flexible lenses. The maximum difference between two measurements of AC depth on the same eye under the same conditions was 0·15 mm. The average difference was 0·0825 mm for rigid lenses and 0·1 mm for flexible lenses.

Figure 5B shows the correlation between the two estimates of refraction on the same two visits, with r=0·96 for rigid lenses and r=0.98 for flexible PolyHEMA lenses. The largest difference between successive refractions of the same eye under the same conditions was 1·00 D, with an average difference of 0·24 D for rigid lenses of 0·39 D for soft lenses.

## Discussion

The normal crystalline human lens changes refractive power by alteration in shape. As ciliary muscle tone increases and the tension on the lens zonule decreases, the elasticity of the lens capsule causes it to assume a more spherical shape.[5] In the course of this change of shape the anterior surface of the lens moves forward and the anterior chamber shallows. It has been calculated that for a refractive change of 6·00 D the anterior surface of the lens moves by 0·401 mm[6] during the alteration in shape of the lens which changes the refractive power of the eye.

It is known that pilocarpine can induce an accommodative effort in man.[7] In a similar fashion, experimental work with injectable lenses in monkeys shows shallowing of the anterior chamber after pilocarpine administration to stimulate the ciliary body.[1]

For conventional 'in the bag' implants the putative mechanism of pseudophakic

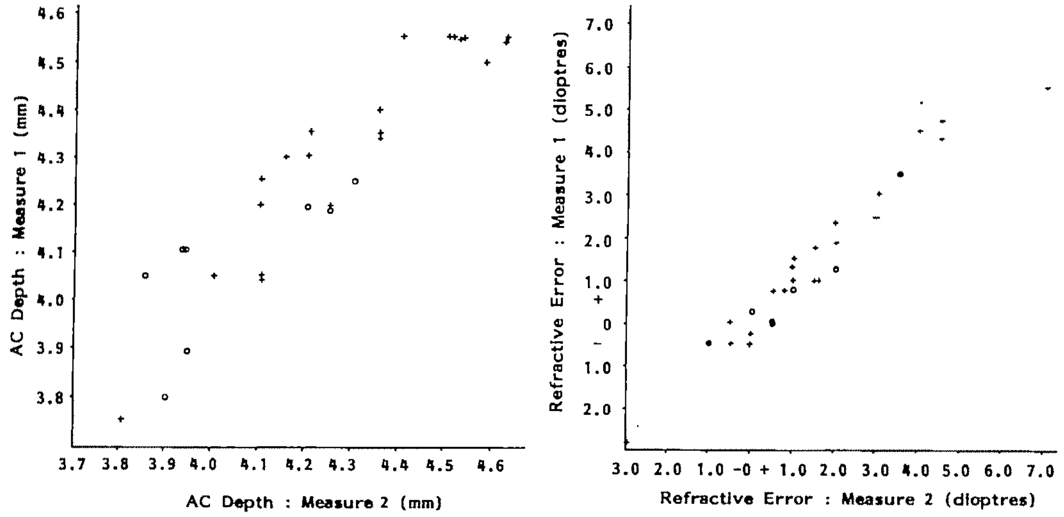

*Fig. 5A* *Fig. 5B*

*Figure 5: Reproducibility of measurements made on two separate occasions.*
*Rigid lenses are shown as +.*
*Flexible lenses are shown as o.*
*5A shows anterior chamber depth measurement.*
*5B shows refraction measurements.*

accommodation is different in that it involves a forward shift of the entire implant rather the change in lens shape which the natural lens achieves. The Binkhorst formula for calculation of implant power[8] has been criticised in that it requires an estimate of the anticipated AC depth with the implant in situ.[9] It is a useful formula, however, for calculation of the exact change in implant position required to produce a specified change in refraction, provided other factors are constant. With this formula for a posterior chamber lens implanted into an eye of normal axial length (23 mm) and corneal curvature (7·46 mm) the anterior chamber depth must decrease by 2 mm to provide a change of 3.00 D.

Our results do not show a shift in lens position of more than 0.25 mm even when the situation of maximal ciliary muscle stimulation (after pilocarpine) is compared with maximal ciliary muscle relaxation (after cyclopentolate). With the Binkhorst formula this change in AC depth would account only for 0.37 D of accommodation, and is seen only with rigid tripod lenses. (Hydrogel lenses do not show any tendency to move at all. No obvious reason for this difference between the two lens types is apparent from our experiment.) In the study there was no detectable increase in refraction to accompany the movement of the rigid lenses.

Despite this lack of optically significant lens movement Table 1 shows that five eyes at least had near vision of N8 or better with distance correction only that most could read at a distance of less than 35 cm.

This result has several possible explanations. It might be that the methods of measurement used in our study were not sensitive or reliable enough to detect the lens movement. The estimate of internal reliability shows that this is not the case. Our average difference in AC depths on two occasions was 0·0825 for the rigid lenses. While not as accurate as the best documented test of reliability with the Haag-Streit pachymeter on normal eyes,[10] where an average difference of only 0.037 mm was recorded, this is evidently sufficient to detect any optically important changes. The measurement of refraction in our study also shows good internal consistency (Fig 5B). Ideally the use of an autorefractor would be preferable to retinoscopic refraction, but autorefractors are not reliable with the small pupil size produced by pilocarpine.[11]

There must therefore be some other way to explain the phenomenon of apparent accommodation. The influence of gravity on the IOL was excluded by the study design. We do not know whether it could significantly affect lens position. Further work is required to confirm or refute this for bag supported implants. Anterior chamber lenses have been shown not to move under gravity.[12]

Optical considerations have been suggested in the past.[2] The pupil size may affect the depth of focus (the distance in front of or behind the retina at which a focused image is projected.[13] Down to 3 mm the depth of focus increases with decrease in pupil size because of the pinhole effect. Below this size diffraction lowers the depth of focus again.[14] Pupil size was not recorded in our study. Mixed astigmatism of the cornea may explain a large depth of focus, as it creates a conoid of Sturm which straddles the retinal plane.[15] In Table 1 eyes 8, 10 and 13 all show this effect.

This project therefore shows little evidence that lens movement contributes to pseudophakic apparent accommodation, which seems most likely to be due to a combination of optical factors. For clarity the phenomenon is better referred to simply as depth of focus, as this does not imply an active mechanism of accommodation.

Both rigid and flexible posterior chamber implants appear to be stable in the antero-posterior direction under all conditions of ciliary muscle stimulation in our patients. It could be that in our study group the patients are too old on average to have much accommodative effort in the ciliary muscle. However, Fisher has shown that accommodative effort in the ciliary muscle actually increases up to middle age,[5] and that presbyopia is due to increase in the rigidity of the lens substance.[16] It is thus not likely that instability of a similar implant would present problems even in a younger age group.

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# *Bacillus*-induced endophthalmitis: new series of 10 cases and review of the literature

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## Abstract

**We reviewed the charts of 10 patients who were admitted to the Massachusetts Eye and Ear Infirmary over a 10-year period with the diagnosis of *Bacillus* species endophthalmitis. To our knowledge this is the largest single series in the literature and includes the first two reported cases of *Bacillus* endophthalmitis following glaucoma filtering procedures. Seven cases developed following penetrating ocular trauma. One occurred in an intravenous drug abuser. Five eyes ultimately underwent enucleation; only the two eyes that developed endophthalmitis after elective surgery retained useful vision. Review of the literature indicates that parenteral and intravitreal antibiotic prophylaxis against endophthalmitis after penetrating ocular trauma should include gentamicin, in combination with vancomycin or clindamycin, to provide adequate coverage against infection with *Bacillus* spp., as prognosis is poor once infection is established. *Bacillus* spp. cultured from ocular tissues or fluids should not be dismissed as contaminants.**

*Bacillus* spp. are ubiquitous, Gram-positive organisms that can infect ocular and adnexal tissues leading to dacryocystitis, conjunctivitis, keratitis, and iridocyclitis.[1] *Bacillus cereus* can lead to endogenous[2,3] or exogenous[4-13] endophthalmitis. Intraocular infections with this and other *Bacillus* spp. rapidly progress to panophthalmitis necessitating enucleation.[2-7,9-11,13]

A review of our cases and the literature indicates an increased incidence of *Bacillus*-induced endophthalmitis. We describe features of the trauma and the appearance of the eye that should alert the ophthalmologist to the possibility of infection with *Bacillus*, provide insights to the pathogenesis, and review strategies for prophylaxis and treatment.

## Subjects and methods

The bacteriology log books of the Porter Bacteriology Laboratory of the Massachusetts Eye and Ear Infirmary were reviewed for *Bacillus*-induced endophthalmitis cases diagnosed between October 1978 and February 1989. Diagnosis was based on culture of *Bacillus* spp. from the ocular surface and/or intraocular fluids of patients with endophthalmitis. Eleven cases were identified. The charts of 10 were located. Follow-up information was obtained through questionnaires distributed to the patients' ophthalmologists.

## Results

Data from the charts of the 10 patients are summarised in Tables I and II. All except patient eight (see below) were healthy males.

Only patients nine and 10 had had previous ocular disease. Patient nine had undergone a filtering procedure two months prior to the onset of endophthalmitis; patient 10 had undergone multiple ocular operations (see case two below). Neither of these patients had a history of ocular trauma. Visual outcome was good in both cases: patient nine achieved a visual acuity (VA) of 20/30, patient 10 achieved 20/50.

Patients 1–7 presented after penetrating ocular trauma. Five had an associated intraocular foreign body (IOFB), metallic in four cases and stone in one. The other two cases followed trauma with metallic objects without an associated IOFB on presentation.

All lacerations were sutured primarily and prophylactic antibiotics were given (Table II). In all cases following trauma the antibiotics were

TABLE I *Cases of* Bacillus*-induced endophthalmitis*

| *Patient/age/sex* | *Eye* | *Route of infection* | *IOFB** | *Culture site* | *Organisms cultured* | *VA†* | *Outcome* |
|---|---|---|---|---|---|---|---|
| 1/21/M | OS | Trauma | metal | vitreous | *Bacillus* spp. | LP‡ | NLP§ |
| 2/27/M | OS | Trauma | metal | vitreous<br>aqueous | *B. cereus* | LP | Enucleation |
| 3/19/M | OD | Trauma | rock | vitreous | *Bacillus* spp.<br>*Enterobacter* | LP | 20/400 |
| 4/20/M | OD | Trauma | metal | vitreous | *B. cereus* | HM | Enucleation |
| 5/42/M | OS | Trauma | NO | vitreous | *B. cereus* | LP | LP |
| 6/49/M | OS | Trauma | metal | wound<br>conjunctiva | *Bacillus* spp. | LP | Enucleation |
| 7/15/M | OS | Trauma | NO | vitreous<br>iris | *Bacillus* spp. | 20/50 | Enucleation |
| 8/40/M | OS | IV drug | NO | vitreous | *B. cereus* | NA¶ | Enucleation |
| 9/50/M | OS | Filter | NO | aqueous | *Bacillus* spp.<br>*S. epidermidis* | NA | 20/30 |
| 10/80/M | OS | Filter | NO | aqueous | *Bacillus* spp. | 20/200 | 20/50 |

*Intraocular foreign body.
†Visual acuity on initial presentation.
‡Light perception.
§No light perception.
¶Not available.

TABLE II *Cases of* Bacillus-*induced endophthalmitis*

| *Patient* | *Initial antibiotics** | | | | *Time started after diagnosis (h)* |
|---|---|---|---|---|---|
| | *Intravenous* | *Subconjunctival* | *Topical* | *Intravitreal* | |
| 1 | Cephalothin 4 g,<br>gentamicin 240 mg | – | Chloroptic<br>gentamicin | – | 8 h |
| 2 | Cephalothin 4 g,<br>gentamicin 240 mg | – | – | – | 6 h |
| 3 | Cephalothin 12 g,<br>gentamicin 240 mg | – | Erythromycin | – | 6 h |
| 4 | Cephalothin 4 g,<br>gentamicin 240 mg | Cephalothin,<br>gentamicin | Tobramycin,<br>polymyxin-B,<br>polysporin | – | 6 h |
| 5 | Cephalothin 4 g,<br>gentamicin 240 mg | – | – | Clindamycin 1 g,<br>gentamicin 400 mg | 6 h |
| 6 | Cephalothin 4 g,<br>gentamicin 180 mg | – | Cephazolin<br>gentamicin,<br>polymyxin-B,<br>polysporin | – | 10 h |
| 7 | Ampicillin 1 g,<br>gentamicin 120 mg | – | – | – | 6 h |
| 8 | Clindamycin 1·8 g,<br>vancomycin 2·4 g,<br>gentamicin 120 mg | Gentamicin | Cephazolin,<br>tobramycin | Vancomycin 1 g,<br>clindamycin 1 g<br>gentamicin 400 mg | 6 h |
| 9 | Methicillin 6 g,<br>gentamicin 240 mg | Methicillin,<br>gentamicin | Bacitracin,<br>neosporin | – | 6 h |
| 10 | Cephalothin 4 g,<br>gentamicin 180 mg | Cephalothin,<br>gentamicin | Cephazolin,<br>gentamicin | – | 6 h |

*On admission to the Massachusetts Eye and Ear Infirmary.

started within 11 hours of the trauma. None received clindamycin or vancomycin on admission. Clindamycin was added intravenously (IV) to the antibiotic regimen of patients two and seven 24 hours after the diagnosis of endophthalmitis; vancomycin was added topically to patient two 24 hours after diagnosis.

Patient five received intravitreal gentamicin and clindamycin on presentation, and vancomycin four days after admission; none of the other patients with ocular trauma received intravitreal antibiotics initially. Intravitreal cephazolin and gentamicin were administered to patients four and seven two days after admission.

The onset of the endophthalmitis occurred within 24 hours of the trauma in two patients, and within 48 hours in five.

Vision was lost in all cases following trauma (except patient three, who retained a VA of 20/400) regardless of the prophylactic and therapeutic measures.

Endophthalmitis developed in a 40-year-old-man (patient eight), an IV drug abuser and alcoholic without a history of ocular trauma or ocular surgery. Presentation resembled that in the cases the followed trauma (see below). Despite early (four hours after onset of symptoms) and vigorous intravitreal and systemic combinations of clindamycin, vancomycin, and gentamicin, the condition of the eye deteriorated rapidly, and enucleation was performed one week later.

The onset of the endophthalmitis was explosive in all cases following trauma and in the IV drug abuser, with severe chemosis, pain, injection, proptosis, corneal ring abscess, and pus in the anterior chamber. The presentation was milder in the cases that followed intraocular surgery lacking the above signs. No patient developed fever or leucocytosis.

*Bacillus* spp. were cultured in all cases, and in cases two, four, five, seven and eight *B. cereus* was identified. Antibiotic susceptibilities were available for eight of the isolates (Table III).

## CASE 1

A 27-year-old white man (patient two) presented to another hospital on 12 April 1988 after a penetrating injury to the left eye. He had been striking steel against steel. A metallic IOFB was removed, the corneal laceration was repaired, and he was started on IV cephalothin and gentamicin. No cultures were taken and no intraocular antibiotics administered. On 13 April 1988 he was transferred to the Massachusetts Eye and Ear Infirmary. The right eye was normal. The left eye had light perception; the eyelids were swollen and red, and severe chemosis and conjunctival injection were present with a purulent discharge (Fig 1). The corneal laceration was dehiscent, with iris tissue prolapse. A corneal ring abscess was present (Fig 2). The anterior chamber had a fibrinous reaction. Proptosis was present. Ultrasound revealed panophthalmitis and retinal detachment but no IOFB. Two hours after presentation vitreous and anterior chamber taps were performed; 200 µg gentamicin and 450 µg clindamycin were injected into the vitreous, and topical tobramycin and cephazolin were started. Appropriate doses of IV tobramycin, and cephalothin were also started. On 14 April 1988 the cultures grew an abundant *Bacillus* sp., later determined to be *B. cereus*, and susceptibilities were determined (Table III). Topical cephazolin and systemic cephalothin were discontinued, topical vancomycin and IV clindamycin were added. The condition of the eye continued to deteriorate with increasing pain; intravitreous injections of clindamycin and gentamicin were repeated. On 16 April 1988 light perception failed and on 19 April the eye was enucleated.

## CASE 2

An 80-year-old white man (patient 10) presented with tearing and redness of the left eye that had started a few days previously. He denied having suffered trauma. The eye had undergone trabeculectomy seven years earlier for medically

TABLE III *Antibacterial susceptibilities of cultured* Bacillus

| *Patient* | *Antibiotics* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Bacitracin* | *Clindamycin* | *Erythromycin* | *Methicillin* | *Penicillin* | *Cephalozin* | *Chloromycetin* | *Gentamicin* | *Vancomycin* |
| 1 | S | R | S | R | R | R | S | S | NT |
| 2 | R | S | S | R | R | R | R | S | S |
| 3 | R | R | S | R | R | R | S | S | NT |
| 4 | R | S | S | R | R | R | R | S | S |
| 5 | R | R | S | S | R | R | R | S | S |
| 7 | R | S | S | R | R | R | S | S | S |
| 8 | R | – | S | R | R | R | S | S | S |
| 10 | S | S | R | S | S | S | S | S | NT |

S=sensitive.
R=resistant.
NT=not tested.

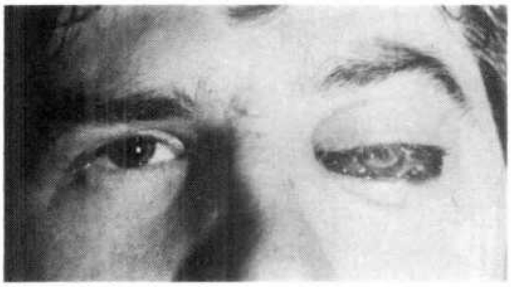

*Figure 1: Infected eye of patient two on presentation, showing proptosis, periorbital swelling, and chemosis.*

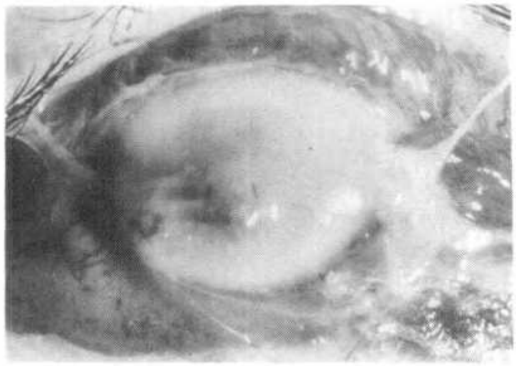

*Figure 2: Eye of patient two showing purulent discharge, chemosis, and a corneal abscess.*

uncontrollable glaucoma. Four years later a bleb revision had been performed, and two years after that an intracapsular cataract extraction had been performed. Two months prior to presentation the visual acuity OS was 20/60; the eye was quiet with a thin functioning bleb without a leak.

On presentation the VA was 20/200 OS. The conjunctiva was 2+ injected superiorly, with mucopurulent discharge. The filtering bleb, anterior chamber, and vitreous were filled with products of inflammation, and the cornea was without an abscess.

Inflammatory cells but no organisms were found in Gram-stained fluid from an anterior chamber tap. An unidentified *Bacillus* was cultured and susceptibilities determined. Subconjunctival, topical, and IV cephalothin and gentamicin were given. Topical prednisolone was added. No intraocular antibiotics were administered. Eight days later the VA was 20/200, eventually 20/50.

## Discussion

*Bacillus* spp. are Gram-positive, facultative, and aerobic rods that are ubiquitous, especially in environments where soil, dust, or animal manure are common.[1,11] Spores produced by *Bacillus* spp. persist in soil for years.[14,15] First recognised in 1891 by Poplawska[4] and subsequently by others[5,6,16] as a cause of destructive endophthalmitis, *Bacillus* spp. are now the second most common cause of endophthalmitis after *Staphylococcus epidermidis* following penetrating ocular trauma.[8,10-13] Whether this reflects an increased incidence of *Bacillus*-induced endophthalmitis or improved reporting is uncertain. While *B. subtilis* dominated earlier reports of *Bacillus*-induced endophthalmitis, more recent reports have stressed the occurrence of *B. cereus*, with scattered case reports of endophthalmitis secondary to *B. licheniformis* and *B. laterosporus*.[13,17,18] Five of our cultures were identified as *B. cereus*.

*B. cereus* produces a unique exotoxin in addition to enterotoxins, phospholipase C, haemolysins, proteolytic enzymes, and bacteriolytic enzymes, and is resistant to lysozymes.[15] These might explain the ocular destruction caused by the organism. However, other factors must play a part in the pathogenicity of *Bacillus* spp. since the non-toxin producing *B. licheniformis* can also cause severe, vision-threatening endophthalmitis.[17]

The rapid progression and destructive nature of endophthalmitis caused by *Bacillus* pose a problem for the ophthalmologist. All series reported so far, including ours, show a consistently poor outcome when treatment was begun after the identification of *Bacillus* as the cause. The only exceptions are our two cases that followed surgery and the case reported by Schemmer and Driebe in 1987,[12] where early, *Bacillus*-specific, vigorous treatment was successful in saving useful vision.

Endophthalmitis secondary to *B. cereus* after trauma or in IV drug abusers typically presents with the rapid onset of proptosis, severe injection, and chemosis. A corneal ring abscess is common,[7,9,11] and hypopyon may be present. Patients may have fever and leucocytosis.[11,17] An IOFB, present in four of our patients, is frequently found and may be contaminated with *Bacillus* spp., or may allow a *Bacillus* sp. that has colonised the conjunctiva (in environments such as farm work) to enter the eye.[19]

In 1901 Romer described one case of *Bacillus*-induced endophthalmitis after intraocular surgery.[20] In 1918 Greenspoon described two such cases occurring 24 hours after cataract surgery resulting in phthisis bulbi.[16] The source of the *Bacillus* was the irrigating solution used during surgery. In contrast, our two postsurgical cases occurred two months and two years after the last surgery and were characterised by a milder onset and better outcome. This could be due to a smaller inoculum or infection with a less virulent *Bacillus* species.

*B. cereus* produces β-lactamases that render it resistant to penicillin-G and the cephalosporins.[1,11] Gentamicin has been shown to offer moderate to good activity against *B. cereus*,[1,21] but alone is not sufficient for therapy of *Bacillus* spp. endophthalmitis. This is supported by our findings and by others'.[7,9,13] Most notably, O'Day *et al*[7,9] reported that endophthalmitis developed despite the use of gentamicin for prophylaxis and/or therapy.

Clindamycin has moderate to good activity against *B. cereus*[1] and, when administered subconjunctivally or parenterally, reaches therapeutic levels in the iris, choroid, and vitreous.[22,23]

O'Day *et al* found that control of *B. cereus*-induced endophthalmitis in rabbits was best when clindamycin and gentamicin were administered concomitantly; the action may have been synergistic.[7] This was confirmed by the *in-vitro* work of Gigantelli and coworkers.[24]

Because of the destructive nature of *Bacillus*-induced endophthalmitis and the variable to poor intraocular penetration of most systemically or periocularly administered antibiotics, intravitreal administration is favoured.[25–27] A combination of 200–400 μg of gentamicin and 450 μg of clindamycin is recommended.[25–30] In addition, eight μg/ml gentamicin and nine μg/ml clindamycin can be added to the vitrectomy infusion fluid.[31]

Experimental results indicate that gentamicin and vancomycin are another effective antibiotic combination.[32] *B. cereus* is highly sensitive to vancomycin,[1] which produces no significant ocular toxicity when injected into the vitreous of rabbit eyes in doses up to 2 g. Vancomycin may act additively or synergistically with aminoglycosides against Gram-positive organisms.[32]

Topical and intravenous gentamicin, vancomycin, and clindamycin are also administered. Serum levels of the antibiotics and the appropriate haematological and urine parameters should be carefully monitored to prevent adverse effects.[33]

Intravitreal dexamethasone (to control the destructive inflammation)[26–29 34] and early vitrectomy[25–27 30] have recently been recommended in the management of sight threatening endophthalmitis such as that induced by *B. cereus*.

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# Central retinal vein occlusion in people aged 40 years or less: a review of 17 patients

R F Walters, D J Spalton

## Abstract

**Seventeen patients with central retinal vein occlusion aged 40 or under were reviewed. Ocular involvement was characteristically unilateral, with moderate degrees of retinal haemorrhage, little retinal ischaemia, and a tendency to optic disc swelling. Visual prognosis was good. Follow-up showed that most patients have good general health and no involvement of the fellow eye. There was little evidence to support an inflammatory aetiology or underlying vascular disease in most of the patients. An alternative explanation for the development of CRVO in young patients might be a congenital anomaly of the central retinal vein.**

Central retinal vein occlusion (CRVO) is usually seen as a disease of the elderly, when it is frequently associated with arteriosclerotic or atherogenic disease elsewhere, glaucoma, or factors which affect blood coagulability and viscosity. It is less common in younger people. In two large studies[1,2] of CRVO 11 of 116 patients (10%) and approximately 14 of 179 patients (8%) were aged 40 years or less.

Attention was first focused on these younger patients by Lyle and Wybar[3] in 1961, who described seven patients, though on review probably only five of these had CRVO. These patients ranged in age from 24 to 49 years. The authors drew attention to the characteristic fundal appearances of unilateral disc swelling, namely, venous dilatation and peripheral retinal haemorrhages in the presence of good visual acuity. They emphasised a male preponderance and the fact that the patients were otherwise well and made a full visual recovery. Three patients were followed up for 3, 5, and 6 years respectively and suffered no further problems. In the absence of overt causes for the CRVO they postulated that a vasculitis of the central retinal vein was responsible, making an analogy with Eales' disease.

This report was followed by another description of five cases by Lonn and Hoyt,[4] who coined the term 'papillophlebitis'. They thought the aetiology was inflammatory on the grounds that whitish sheathing of the retinal veins adjacent to the optic disc could be seen after the swelling had subsided. Soon afterwards further cases were published by Cogan,[5] Hart *et al*,[6] and Hayreh.[7] The last two reports published fluorescein angiograms showing that the appearances were not dissimilar to those of non-ischaemic CRVO in older patients. Hart *et al* postulated that the better visual prognosis was due to the absence of associated arterial disease. All these authors, however, subscribed to the view of an inflammatory aetiology, though direct evidence to support this concept is lacking.

Premature vascular disease is always a worrying finding both for the physician and the patient. We have retrospectively reviewed 17 patients, aged 40 years or younger who presented with a CRVO, with a view to seeking the underlying aetiology and to ascertain the general and visual prognosis.

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## Material and methods

From the diagnostic index for fundus photography at St Thomas's Hospital we identified 182 patients diagnosed as having a central retinal vein occlusion between 1968 and 1984. This would be only a proportion of the patients seen with this condition at the hospital, as fundus photography is not routinely performed on all patients. Of the 182 patients 142 had adequate documentation for the purpose of this study.

From the hospital records we identified the date of presentation and age of the patients. Twenty-one patients were aged 40 or under at presentation, and these were selected for special study. Both records and colour photographs were available for only 17, and most of these had also had fluorescein angiography (Table I). Particular attention was paid on review of the notes to any evidence of systemic disease on presentation and to the presence of possible aetiological factors such as hypertension, smoking, diabetes mellitus, the contraceptive pill, and a family history of vascular disease. As this was a retrospective study full data were not available for all patients, and these findings are summarised (Table II) together with the results of investigations at presentation (Table III).

Central retinal vein occlusion was defined as venous dilatation with retinal haemorrhages scattered throughout the fundus to the periphery. The severity of the retinopathy was

TABLE I *Details of the 17 patients studied in depth*

| *Patient* | *Age* | *Sex* | *Date of onset* |
|---|---|---|---|
| A | 28 | F | Jan 1976 |
| B | 38 | F | Mar 1981 |
| C | 37 | F | July 1975 |
| D | 38 | M | Jan 1979 |
| E | 28 | F | Jan 1975 |
| F | 33 | M | Oct 1980 |
| G | 33 | F | Oct 1976 |
| H | 33 | M | Dec 1975 |
| I | 34 | M | Sept 1978 |
| J | 37 | M | July 1973 |
| K | 22 | M | Mar 1979 |
| L | 23 | F | Aug 1982 |
| M | 28 | M | Dec 1983 |
| N | 39 | F | June 1979 |
| O | 35 | M | Oct 1974 |
| P | 35 | M | Oct 1979 |
| Q | 14 | M | Nov 1981 |

Average age = 31·5 years. Male/female ratio = 10:7.

TABLE II *Possible predisposing factors in the 17 patients studied*

| *Patient* | *Systemic hyper-tension* | *Diabetes mellitus* | *Smoker* | *Contra-ceptive pill* | *Vascular disease* | *Ocular disease* | *Other systemic disease* |
|---|---|---|---|---|---|---|---|
| A | – | – | – | – | – | – | Asthma |
| B | – | + | – | + | – | – | – |
| C | – | + | – | – | Raynaud's phenomenon | – | – |
| D | – | – | + | NR | – | Ocular hyper-tension | – |
| E | – | – | – | – | Migraine | – | Mitochondrial myopathy (later) |
| F | – | – | + | NR | – | Anterior uveitis | Ankylosing spondylitis |
| G | – | – | – | – | – | – | Iron deficiency anaemia |
| H | – | – | + | NR | – | – | – |
| I | – | – | Gave up 2 years ago | NR | – | – | – |
| J | – | – | – | NR | Migraine | – | – |
| K | – | – | + | NR | – | – | – |
| L | – | – | – | + | – | – | – |
| M | – | – | – | NR | – | – | – |
| N | – | – | NK | – | – | – | – |
| O | – | – | – | NR | – | – | – |
| P | – | NK | NK | NR | – | – | – |
| Q | – | – | – | NR | – | – | Non-specific immunological illness |

+=Present. –=Absent. NK=not known. NR=not relevant.

assessed by grading the physical signs seen on the fundus photography and fluorescein angiogram as follows: (*a*) the degree of retinal haemorrhage (on scale 1–5); (*b*) the degree of optic disc swelling (on scale 0–4); and (*c*) the degree of retinal ischaemia (on scale 0–4). Associated other findings, such as cilioretinal artery occlusion and disc cupping were noted separately.

All 17 patients were sent a follow-up questionnaire by post and replies were received from nine. This questionnaire sought to elicit a more detailed history of the atherogenic factors at the time of the initial illness and to inquire about the visual recovery or further problems with their vision or general health since presentation.

## Results

The average age of the 142 patients was 58·6 years, with 82 men (average age 60·2 years) and 58 women (average age 56·2 years). The sex of two patients could not be ascertained with certainty from the records. These were over 40 and are included in the overall data but omitted from

TABLE III *Summary of investigations*

|  | *FBC* | *ESR (mm/h)* | *Plasma fibrinogen normal range (2·0–4.0 g/l)* | *Serum proteins* | *Serum choles-terol* | *Serum tri-glyceride* | *VDRL TPHA* | *Random blood sugar* | *CXR* | *Others* |
|---|---|---|---|---|---|---|---|---|---|---|
| A | N | 4 | NK | N | NK | NK | NK | N | NK |  |
| B | N | 4 | NK | NK | NK | NK | NK | N (DM) | NK |  |
| C | N | 13 | NK | NK | N | N | −ve | (DM) | N |  |
| D | N | 14 | N | N | N | N | −ve | N | N | Sicklecell −ve |
| E | N | 15 | N | N | N | N | NK | N | NK | +ve ANF 1:250 |
| F | N | 11 | N | N | NK | NK | −ve | N | NK | HLA B27 +ve |
| G | ↓ (9·0 g/dl) | 5 | N | N | NK | NK | NK | N | NK |  |
| H | N | 2 | N | N | N | N | −ve | N | N | +ve ANF 1:10 |
| I | N | 6 | N | N | N | N | −ve | N | NK |  |
| J | N | 12 | NK | N | NK | NK | NK | N | N |  |
| K | N | 1 | N | N | N | N | −ve | N | N |  |
| L | N | 4 | N | N | NK | NK | −ve | N | N | ANF −ve |
| M | N | 4 | NK | N | N | N | NK | NK | NK |  |
| N | N | NK | NK | N | NK | NK | NK | NK | NK |  |
| O | N | 18 | N | N | N | N | −ve | N | N | ANF −ve |
| P | NK | NK | NK | NK | NK | NK | NK | NK | NK |  |
| Q | ↓ (10·7 g/dl) | 43 | NK | NK | NK | NK | NK | NK | NK |  |

N=normal. DM=diabetes mellitus. ANF=antinuclear factor test. NK=not known. ↓ =reduced.

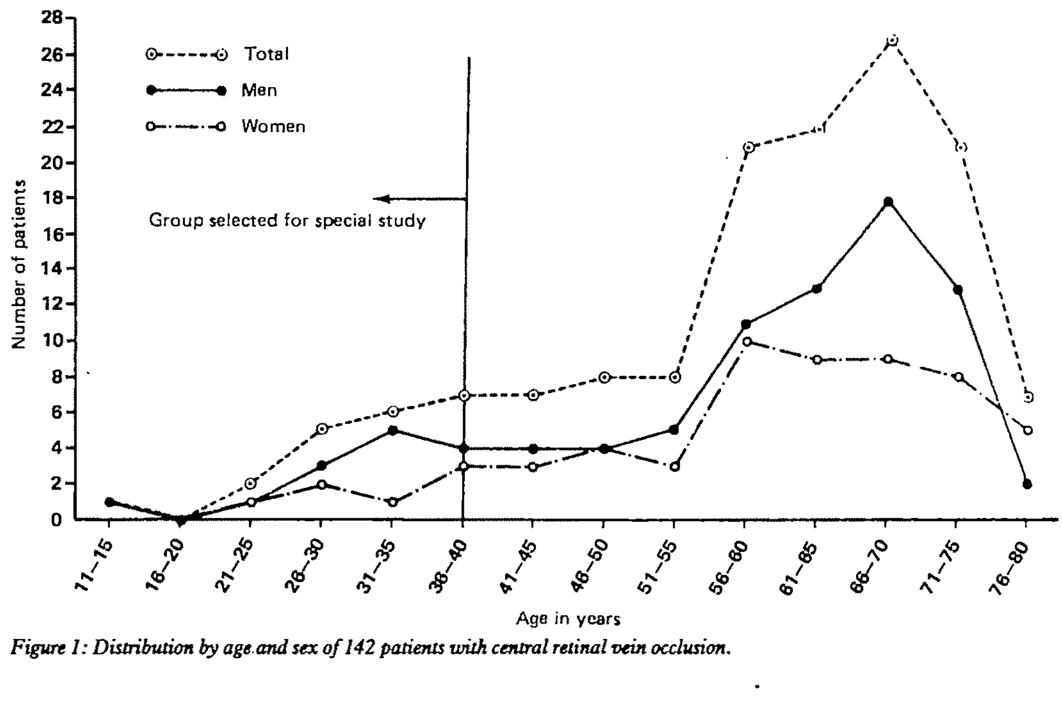

*Figure 1: Distribution by age and sex of 142 patients with central retinal vein occlusion.*

TABLE IV *Assessment of severity of CRVO and visual outcome*

| *Patient* | *Optic disc swelling, grade 0–4* | *Retinal haemorrhage, grade 1–5* | *Degree of retinal ischaemia, grade 0–4* | *VA in affected eye at presentation* | *Latest known* |
|---|---|---|---|---|---|
| A | 2 | 1 | 0 | 6/6 | 6/6 |
| B | 3 | 3 | 0 | 6/60 | 6/18 |
| C | 0 | 2 | 0 | 6/5 | NK |
| D | 0 | 3 | 0 | 6/5 | 6/5 |
| E | 2 | 3 | 1 | 6/24 | 6/5 |
| F | 3 | 3 | 1 | 6/24 | 6/36 |
| G | 0 | 1 | 0 | 6/5 | 6/5 |
| H | 4 | 5 | 3 | C.F | C.F |
| I | 0 | 1 | 0 | 6/9 | 6/6 |
| J | 2 | 3 | 1 | 6/4 | NK |
| K | 1 | 1 | 0 | C.F | NK |
| L | 0 | 1 | 0 | 6/5 | NK |
| M | 1 | 1 | 0 | 6/36 | 6/9 |
| N | 3 | 2 | 0 | 6/36 | NK |
| O | 3 | 3 | 0 | 6/60 | 6/5 |
| P | 0 | 3 | 0 | 6/9 | NK |
| Q | 2 | 3 | 0 | P.L | 6/24 |

NK = not known.

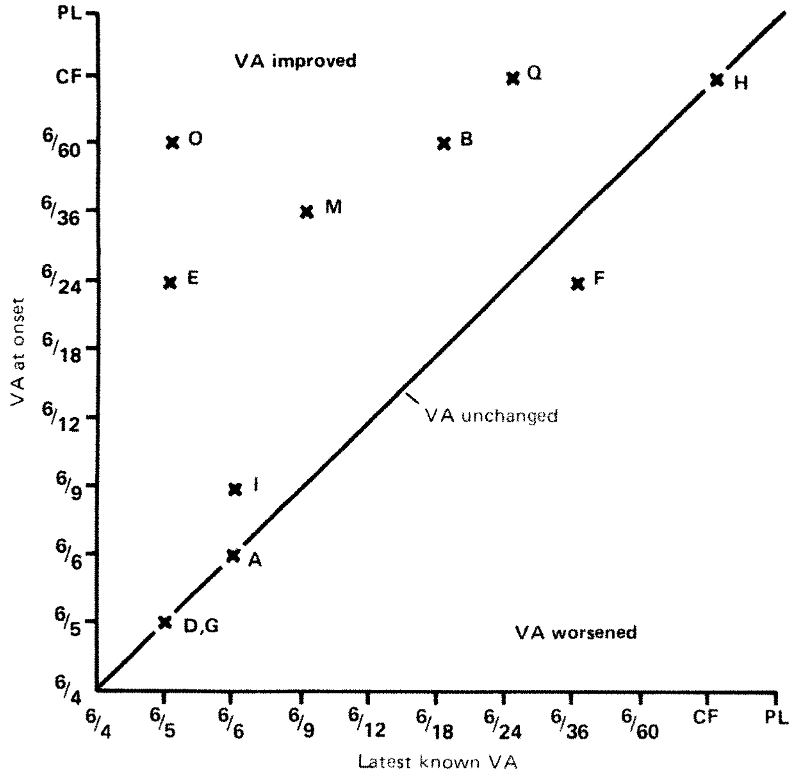

*Figure 2: Visual prognosis of the 11 patients with follow-up data (data not available for remaining six patients).*

TABLE V *Summary of follow-up times and possible aetiological factors*

| *Patient* | *Length of follow-up* | *Comments* | *Known possible thrombotic or atherogenic factors* |
|---|---|---|---|
| *A | 9 years 2 months | Had CVA 8 years later | – |
| *B | 4 years | – | Diabetic (poor control). Pill. FH of hypertention and heart disease |
| C | None | Raynaud's disease | Diabetic |
| D | 5 years 7 months | Ocular hypertension | Smoker |
| E | 9 years 4 months | Migraine. Diagnosed mitochondrial myopathy 2 years later | – |
| *F | 4 years 6 months | Ankylosing spondylitis. Iritis | Smoker |
| *G | 8 years 5 months | Developed gall stones. Iron deficiency anaemia (9·0 g/dl) Positive ANF (1:250) | Overweight. FH of heart disease |
| *H | 9 years 3 months | Positive ANF (1:10) | Smoker. FH of hypertension |
| *I | 6 years 6 months | – | Smoker until 2 years previously |
| J | 7 months | Migraine | – |
| K | None | – | Smoker |
| L | None | Asthmatic | Pill |
| *M | 1 year 3 months | – | FH of hypertension and heart disease |
| *N | 5 years 9 months | Developed gall stones | – |
| O | 1 year | – | Overweight |
| *P | 5 years 5 months | – | FH of heart disease |
| Q | 2 years 6 months | 1 year later CRVO in other eye. Non-specific immunological illness | – |

FH = family history. ANF = antinuclear factor test. *Those who replied to questionnaire.

the male/female ratios. The distribution of CRVO by age and sex is shown in Figure 1.

Twenty-one patients (14·8%) were aged 40 years or younger. Of the 17 with full data available the average age was 31·5 years, with 10 men (average age 32·9 years) and 7 women (average 30·9 years). The age and sex distribution of these patients is shown in Figure 1 prior to the demarcation line. Of these 17 patients 12 were Caucasian, 2 Asian, 2 Negro, and 1 Arabic, which probably reflects the local population mixture at this time.

Tables I to III summarise epidemiological data, systemic associations, and investigations. Table IV and Figure 2 summarise the ocular findings and visual prognosis. Most patients had mild degrees of retinal haemorrhage, little retinal ischaemia, and a tendency to optic disc swelling with a good visual prognosis. Seven patients of the 17 had a presenting visual acuity in the affected eye of 6/36 or worse. Of these, two (patients K and Q) also had cilioretinal artery occlusion and O had an occlusion of the macular branch of the superotemporal arteriole. B (a diabetic) had macular exudates (no diabetic changes in the fellow eye), and the remaining three (H, M, N) all had macular oedema. The visual prognosis was in general good (Table IV and Figure 2), and only two patients (F, H) of the 11 patients for whom data were available were known to have a VA in the affected eye of 6/36 or less on follow-up. Of these, F's visual deterioration was probably due to his anterior uveitis (he had ankylosing spondylitis), and H had macular oedema at presentation. Seven of these 11 patients had a follow-up VA of 6/9 or better. Other notable ocular features were a tendency to optic disc swelling (11 out of 17) and a paucity of signs of retinal ischaemia (in only four patients, and this was comparitively mild), with no patients developing rubeosis iridis. Only one person had raised intraocular pressures (24, 17 mmHg), and none had overt glaucoma.

As this was a selected group from a retrospective study, the information on systemic associations and abnormal investigations at presentation was not complete in all cases. However, because of their relative youth most were investigated carefully. Factors which are associated with atherogenesis or thrombosis (diabetes mellitus, smoking, obesity, contraceptive pill) were found in 10 patients (Table V), and if a family history of heart disease is taken as a predisposition to atherogenesis a further two patients would be included. Two patients also had an immunological illness – F with ankylosing spondylitis and Q with non-specific systemic evidence of immune disease. No patients had systemic hypertension or known abnormal lipid profiles (8 out of 17 were investigated for lipid abnormalities). At presentation G had a positive antinuclear factor test (ANF = 1:250) and an iron deficiency anaemia (9·0 g/dl). He later developed a right ptosis and ophthalmoparesis which was ascribed to a mitochondrial myopathy.

The follow-up postal questionnaire provided useful information (Table VI) and extended the average follow-up time from 35·3 months to 60·9 months (range 6 months to 9 years 3 months). Of the nine patients who responded to the question-

TABLE VI *Result of follow-up questionnaire*

| *Patient* | *Length of follow-up* | *Atherogenic factors at at onset* | *Weight* | *Family history* | *Subsequent general health* | *Prognosis of affected eye* | *Other ocular problems* |
|---|---|---|---|---|---|---|---|
| A | 9 yr 4 m | Nil | Normal | Nil | CVA 8 yr later | Improved | Hemianopia |
| B | 4 yr | Diabetes | Normal | Heart disease + hypertension in father | Good | Poor | Nil |
| F | 4 yr 6 m | Smoker | Normal | Heart disease in father | Good | Poor | Ank spond with iritis |
| G | 8 yr 5 m | Nil | Obese | Heart disease in grandmother | Gall stones | Improved | Nil |
| H | 9 yr 3 m | Smoker | Normal | Hypertension in mother | Good | Poor | Nil |
| I | 6 yr 6 m | Smoker | Normal | Not known | Good | Poor | Nil |
| M | 1 yr 3 m | Nil | Mildly Obese | Heart disease + hypertension in father | Good | Improved | Nil |
| N | 5 yr 9 m | Nil | Normal | Nil | Gall stones | Improved | Nil |
| P | 5 yr 9 m | Nil | Normal | | Good | Improved | Nil |

naire, A had a subsequent cerebrovascular accident (with homonymous hemianopia), G and N developed gallstones, and F (with ankylosing spondylitis) had two further attacks of acute anterior uveitis. The other five remained well. None of these nine patients developed disease in the fellow eye.

## Discussion

The mean age of the 142 patients in this study (58·6 years) is similar to that previously found in other studies[8-11] and shows that CRVO is a disease of the elderly, but although CRVO is less common in younger patients it is by no means rare. Of our patients 25% were aged 50 or less and 15% aged 40 or below. This latter percentage compares with 10% in Kohner and Cappin's[1] and 8% in Vannas and Raitta's series[2] (both of these series were unselected). Our patients were derived from a photographic index, and as younger patients are more likely to be referred for photography than older ones this will weight the numbers accordingly and is likely to account for the increased incidence of younger patients in our series.

CRVO in younger patients is probably a different disease from that seen in more elderly patients. Previous authors[3-7 12] have noted the unilaterality of the retinopathy, its good visual prognosis, and, when patients have been followed for any length of time, its good systemic prognosis. These results are compatible with our own study. The typical fundus appearance is of unilateral optic disc swelling with a moderate degree of retinal haemorrhage, but retinal ischaemia of any severity is uncommon. Optic disc swelling in younger patients with CRVO appears to be more common and more marked than in the elderly. The reason for this in the absence of overt ischaemia is not clear but may reflect the greater number of viable axons in a younger eye, with more axoplasm therefore being passed along the optic nerve.

The most serious threat to vision in our series was concomitant occlusion of a cilioretinal artery at presentation, related to compression of that artery by increased tissue pressure within the optic disc. McLeod and Ring[13] found a cilioretinal supply in 26 of 146 cases of CRVO, and in seven of these there were signs of an associated cilioretinal infarct. Poor acuity at presentation tended to correlate with more pronounced optic disc oedema.

Follow-up data on visual recovery were available for 11 of our 17 patients and showed a generally good prognosis (Fig 2, Table IV), as others have found. Macular oedema was responsible for the poor visual recovery in three patients; one of these was associated with acute anterior uveitis and another with cilioretinal artery occlusion. The remaining seven patients (64%) improved to 6/9 or better. No patient developed rubeosis. The good visual prognosis in these patients contrasts with that expected in the elderly. Rubenstein and Jones[14] studied 143 patients aged 30 and over and found that 59% had a visual acuity of 6/18 or worse in the affected eye and 36% less than 6/60.

Only one patient in our series developed disease in the fellow eye during follow-up, and this patient (Q) was in many ways atypical. At 14 years of age he was the youngest patient in the series. He presented with an overt non-specific immunological illness with arthralgia and a CRVO in the left eye, erythrocyte sedimentation rate, anaemia, raised serum globulins, and inflammatory changes seen on a liver biopsy. Five months later he developed a CRVO in the fellow eye. He was treated with systemic steriods, and the retinopathy resolved, eventually leaving him with a visual acuity of 6/6 and 6/24 18 months later, the reduced acuity in the left eye being due to cilioretinal artery occlusion.

Patient Q was the only patient to have evidence of an inflammatory or immunological underlying disease process which might account for the CRVO. Patient F had ankylosing spondylitis, but this is not typically associated with systemic vasculitis and was probably coincidental to the retinopathy. Although 10 patients had conditions that predispose to premature vascular disease, they must be considered in the context of the general incidence in the population, and it is difficult to draw any conclusions that these conditions were responsible for the retinopathy. Indeed the absence of involvement of the fellow eye or the lack of development of other systemic vascular disease on follow-up argues against a premature tendency to arterial disease. Caution must be taken though, as patient A did suffer a cerebrovascular accident eight years later (unfortunately we have no further details of this illness). No patient in our series had systemic hypertension. Dobson and Kritzinger[15] examined 87 patients with CRVO or branch retinal vein occlusion (BRVO), of whom 40 were under 50 years of age. They found a decreased incidence of systemic hypertension in the younger patients (27% of hypertension versus 62% in the over 50s), but 35% of their younger patients had hyperlipidaemia and four were on the contraceptive pill. From this paper it is impossible to differentiate those patients with BRVO where hypertension is a more likely cause from those with a CRVO.

Although eight of our 17 patients had a lipid screen, no abnormality was found in any of them. Other studies of CRVO in young patients have failed to show any carotid arterial disease on doppler ultrasonography[16] or evidence of inflammatory aetiology.[17]. Fruch *et al*[19] studied 11 patients with CRVO under the age of 45. Seven had severe retinal ischaemia, and five of these had diabetes (2), hypertension (4), and systemic lupus erythematosus (1), whereas the four patients without retinal ischaemia had no systemic disease. Priluck *et al*[12] reviewed 42 patients aged 40 years or younger when CRVO was diagnosed. They found no direct evidence that a vasculitis was a contributory factor. Eight (19%) of their patients were found to have a systemic disease (3 with hpyertension, 2 with diabetes mellitus, 1 with valvular heart disease, 1 with polymyositis, and 1 with polycycstic kidneys). The follow-up period for their patients ranged from three to 26 years (average 14 years), and a further eight patients acquired a systemic disease during that time. Two had hypertension, two suffered 'cardiac death', and four had systemic diseases judged to be unrelated to CRVO. They found (as we did) that the visual prognosis tended to be good and that the incidence of involvement of the other eye was minimal (in only two cases).

As to pathology, it seems reasonable to adopt Virchow's approach[19] regarding factors concerned in the causation of thrombosis. These are changes in the vessel wall, changes in the blood flow, and changes in the composition of the blood.

A vasculitis of the venous wall has been frequently cited[5-7 17 21 22] as a primary cause of CRVO in young adults. It does seem improbable, though, that an inflammatory process should be limited to a few millimetres of vein in one optic nerve head. One might expect to find signs of systemic vasculitis or, at the very least, a substantial incidence of bilateral CRVO. Clinical experience in this study and others shows this is not the case in the great majority of patients. Furthermore, there is no real histological evidence to support this concept. It is difficult to obtain material for histopathological study early in the course of the disease. Most eyes obtained have been removed because they were blind and painful owing to the onset of rubeotic glaucoma weeks or months after the CRVO. In these eyes round cell infiltrate of the perivenular area, intramural region, and within the lumen has been observed.[5 21 23] Green *et al*[23] did a histopathological study on two eyes with CRVO (patients aged 32 and 56 years) enucleated within 24 hours of onset. These showed that the acute inflammatory changes expected in any venous thrombosis (polymorphonuclear cell infiltrate) and vasculitis were not thought to be a contributary factor. They went on to study a further 24 cases (aged 44 to 91) enucleated from two weeks to five years after the CRVO, which generally showed a perivenous round cell infiltrate consistent with chronic inflammation. They convincingly argue that this chronic inflammatory infiltrate is the *result* of the CRVO and not the cause. Endothelial cell proliferation has been suggested as a cause of CRVO.[20] Green *et al*[23] again demonstrated this as a frequent finding in longstanding CRVO but not in the acute phase. They state that this endothelial proliferaton is the result of the repair process and not a causative factor.

TABLE VII *Suggested investigations for young patients with CRVO*

| |
|---|
| Full blood count, ESR |
| Plasma viscosity and fibrinogen |
| Urea, electrolytes, plasma proteins (and electrophoresis) |
| Random serum glucose |
| Fasting lipid profile |
| VDRL/TPHA* |
| Autoantibody screen (including anticardiolipin) |
| Electrocardiogram |
| Chest *x*-ray |

*Venereal disease research laboratory test/*Treponema pallidum* haemagglutination test.

Conditions such as hyperlipidaemia, paraproteinaemias, polycythaemia, increased platelet aggregation, and other hyperviscosity or hypercoagulability syndromes which result in changes in the composition of the blood (and its flow) have often been found in association with CRVO. These factors were not a prominent feature in our series but can undoubtedly be associated with CRVO,[9 11 15 24-26] and it is important to exclude them in all young patients. It does, however, appear that most young patients with CRVO have a uniocular loss with a low risk of involvement of the fellow eye, an extremely low chance of any systemic inflammatory illness being found, and a low risk of any underlying vascular or atherogenic disease. Prolonged follow-up in our series and others[3 12] indicates that most patients continue to have excellent general health.

A hypothesis which might explain these findings would be the presence of a congenital anomaly in the central retinal vein at the lamina cribrosa causing turbulent flow and predisposing to thrombus formation.

We consider that young adults with CRVO require comprehensive physical examination and investigation. Our suggestions for these investigations are set out in Table VII.

We are most grateful to Mr T J Ffytche, Mr M D Sanders, and Mr J S Shilling, who kindly allowed us to study patients under their care.

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# Postenucleation orbital radiotherapy for the treatment of malignant melanoma of the choroid with extrascleral extension

P G Hykin, A C E McCartney, P N Plowman, J L Hungerford

## Abstract

**The outcome is reported in 17 patients in whom an eye was enucleated for malignant melanoma of the choroid with extrascleral extension and who subsequently underwent adjuvant external beam radiotherapy to the orbit as the primary treatment of the extraocular spread of their tumour. Extrascleral extension was encapsulated in five, non-encapsulated in two, and had been surgically transected at enucleation in 10 cases. All the patients have been followed up from enucleation to the present day. Orbital recurrence occurred in only one patient. The overall actuarial survival rate was 51% at 5 years, 44% at 10, and 33% at 15 years. A low orbital recurrence rate of 6% compares very favourably with published figures for this event after enucleation for melanoma with extrascleral extension but without radiotherapy. Adjuvant orbital radiotherapy may have a place in the treatment of selected cases of extracleral extension of intraocular malignant melanoma.**

The incidence of extrascleral extension of choroidal malignant melanoma has been reported to be between 8 and 40%.[1-7] Extraocular spread carries a poor prognosis for survival, with an overall mortality rate from melanoma metastases of between 66 and 73% compared with 39% without extrascleral extension.[1,3] There is agreement that massive extraocular spread should be treated by orbital exenteration,[1,3,7,8] but the management of more moderate degrees of extraocular extension of uveal melanoma is controversial.

At Moorfields Eye Hospital and at Saint Bartholomew's Hospital exenteration of the orbit is advised following enucleation for a posterior melanoma with extrascleral extension only when extensive residual tumour is seen in the orbit during the operation. Exenteration is not recommended when an extrascleral nodule of melanoma is seen at operation but is apparently removed complete with the eye. This applies whether the nodule is reported as being encapsulated, non-encapsulated, or transected on subsequent histopathological examination. Instead, adjuvant orbital radiotherapy is advised. No additional therapy is recommended for melanoma invading the sclera or scleral channels or confined to the episclera.

Few ocular oncology centres advocate postenucleation radiotherapy for extrascleral extension of melanoma and little has been published on the results of its use. The object of this report is to present the results of external beam radiotherapy in the treatment of extraocular extension in terms both of local recurrence and of survival and to determine if it has a role in the future management of selected cases.

## Patients and methods

The case notes were reviewed of all patients with extraocular extension of choroidal malignant melanoma treated in the Ocular Oncology Clinics at Moorfields Eye Hospital and St Bartholomew's Hospital and who had received orbital radiotherapy. Patients who had had external beam radiotherapy prior to enucleation or after orbital exenteration were excluded, as were patients with melanoma of the iris or ciliary body and patients with less than five years' follow-up. Between 1964 and 1982 20 consecutive cases fulfilled the criteria for inclusion in the

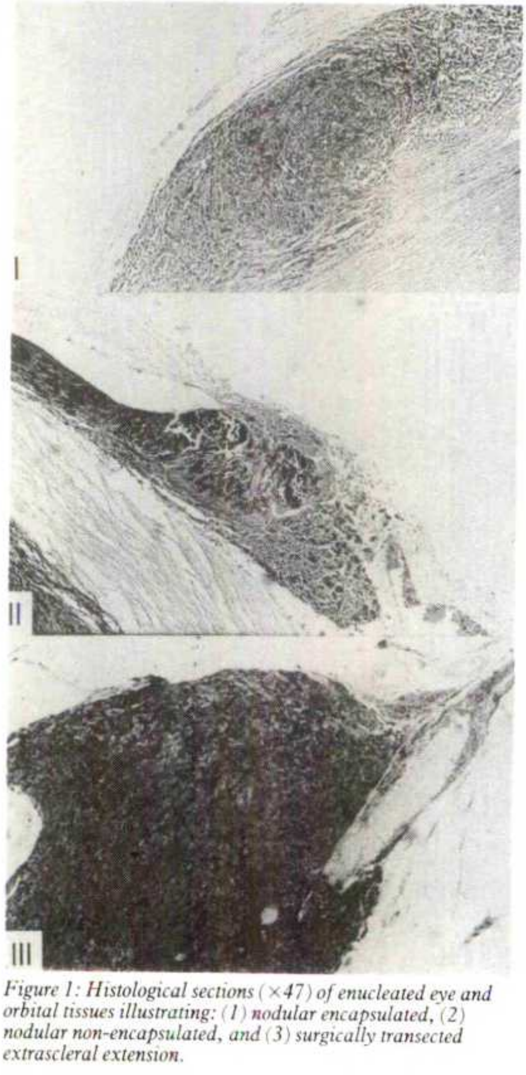

*Figure 1: Histological sections (×47) of enucleated eye and orbital tissues illustrating: (1) nodular encapsulated, (2) nodular non-encapsulated, and (3) surgically transected extrascleral extension.*

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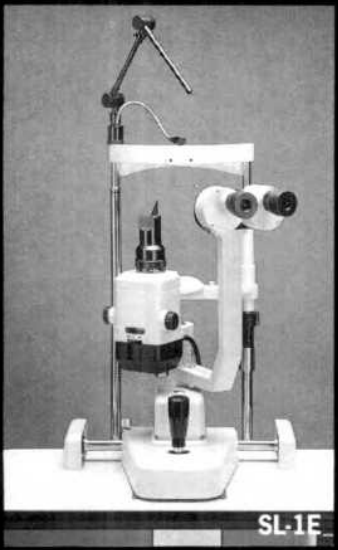

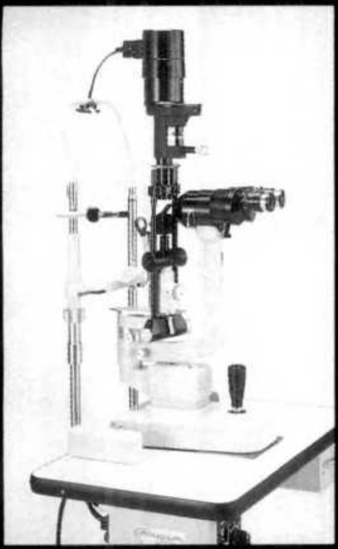

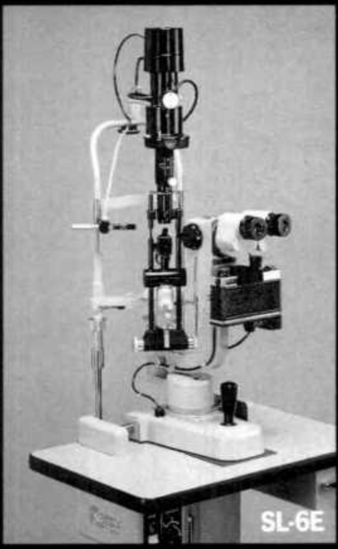

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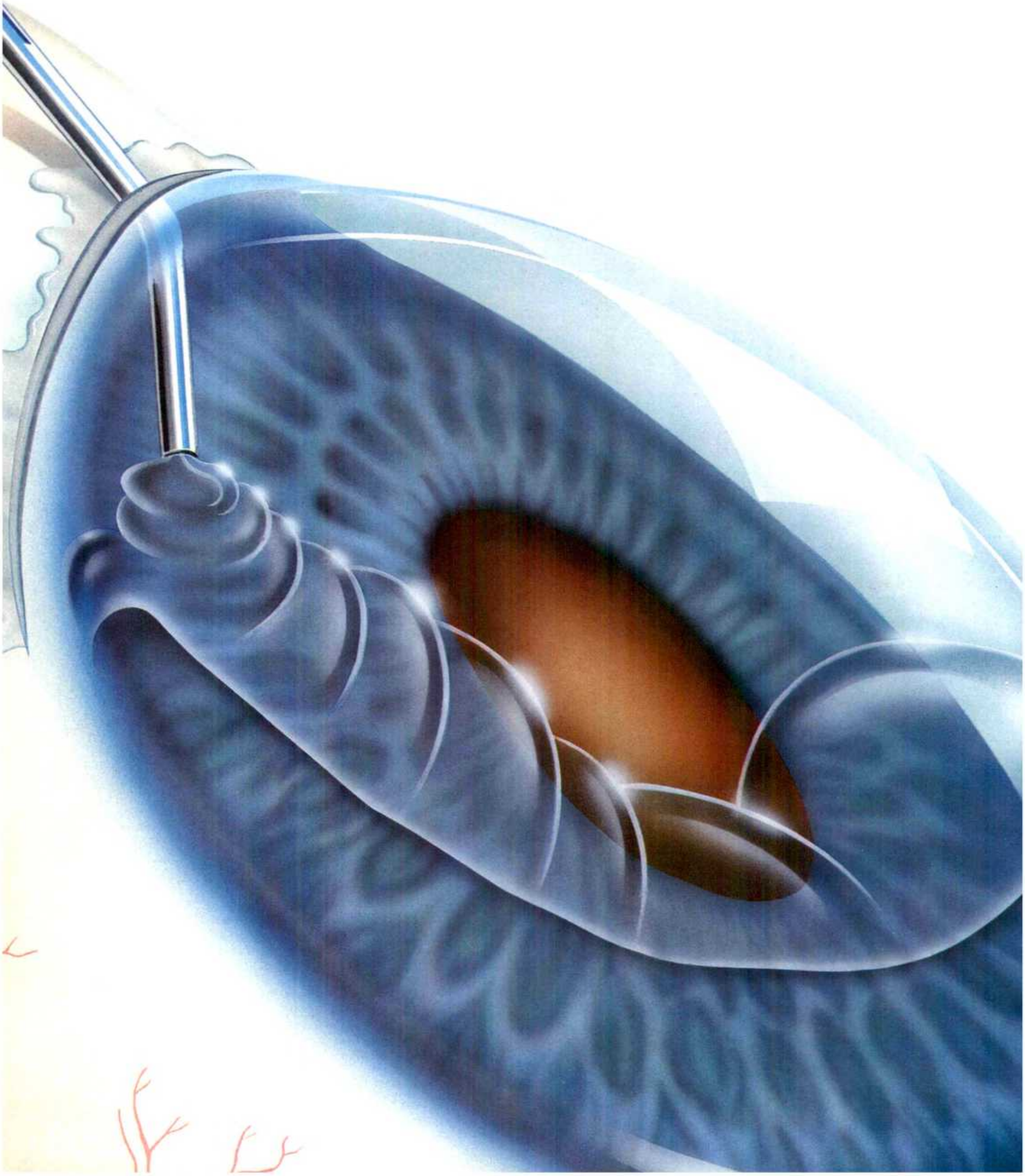

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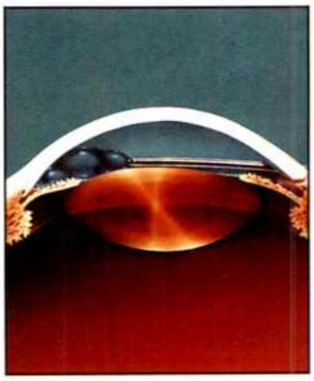
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study, though sufficient follow-up data were not obtained in three. The histology was reviewed in each of the remaining 17 cases, but the data were not analysed for cytological criteria of malignancy. The maximum diameter of the tumour and of the extrascleral deposit was measured. The extrascleral deposit was reported as (1) nodular encapsulated (that is, undisturbed by enucleation), (2) nodular non-encapsulated (not obviously transected, but not encapsulated), or (3) surgically transected (Fig 1).

External beam radiotherapy was given within two months of enucleation. Of 16 patients receiving megavoltage photons, 14 were treated with cobalt-60 and two with caesium-137. One patient was treated with megavoltage electrons. The average prescribed dose was 50 Gy (range 35–60 Gy) in 22 fractions (range 7–33) over a mean of 35 days (range 15–52). All the patients were followed up until the time of death or until the present day, the minimum follow-up being five years. All who are alive have been seen in the last nine months and have had a general and an orbital examination. Gamma glutamyl transferase, liver ultrasound, and bone scan examinations were performed if clinically indicated. Information on deceased patients was obtained from case notes, death certificates, and the United Kingdom Cancer Register. Not all dead patients underwent post-mortem examination. Results were analysed by life table construction and calculation of actuarial survival, and the statistical significance was estimated by Fisher's exact probability test.

## Results

There were 12 male and five female patients. The average age at enucleation was 58·2 years (range 31–71). The histology was spindle cell melanoma in 13 cases and mixed spindle and epithelioid in four. The type of extrascleral extension was nodular encapsulated in five, non-encapsulated in two, and transected in 10 cases. The mean largest diameter of the intraocular tumour was 13·5 mm (range 8–19 mm) and the mean largest diameter of the extrascleral deposit was 3·1 mm (range 2–10·5 mm).

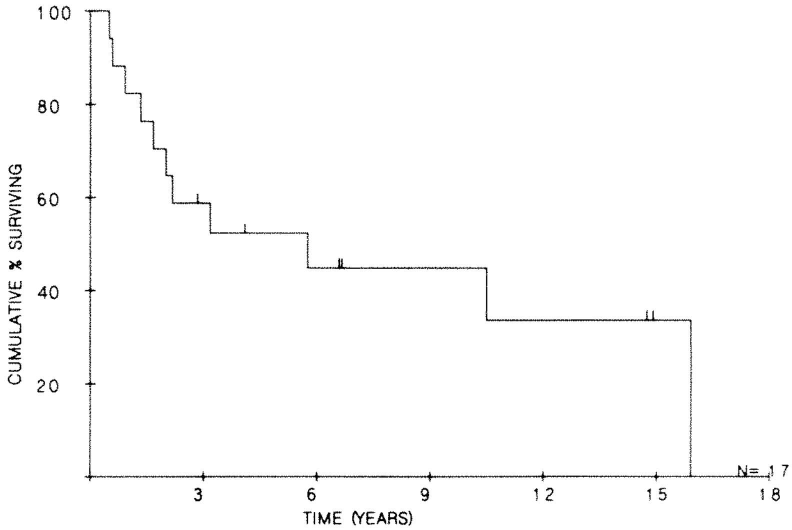

*Figure 2: Actuarial survival curve (17 cases) after enucleation and orbital radiotherapy for malignant melanoma of the choroid with extrascleral extension.*

### SURVIVAL

Fourteen of the 17 patients have died. Eleven died from malignant melanoma metastases, two from cardiorespiratory failure, and one from a primary lung tumour. Three patients are alive and were free of disease when last seen. The actuarial overall survival rate was 51% at 5 years, 44% at 10 years, and 33% at 15 years (Fig 2). There was no significant difference in the survival of patients with transected versus non-transected extraocular spread at 5 and 15 years ($p>0\cdot5$). In addition, in this study the maximum tumour diameter ($>10$ and $\leqslant 10$ mm) and the size of the extraocular spread ($>5$ and $\leqslant 5$ mm) had no statistically significant bearing on survival ($p>0\cdot5$).

### ORBITAL RECURRENCE

One patient developed orbital recurrence. He had undergone enucleation of the right eye at age 66 years, four months after diagnosis of a choroidal melanoma. The tumour was of spindle cell type, and an extrascleral extension was surgically transected at operation. The maximum tumour diameter was 13 mm and maximum diameter of extraocular extension 3·75 mm. 60 Gy megavoltage photons were given in 30 fractions within 50 days of enucleation. Orbital recurrence occurred three weeks after radiotherapy was completed. He then underwent early orbital exenteration but died of disseminated melanoma 20 months later.

## Discussion

Extrascleral extension of choroidal melanoma has a highly significant adverse effect on local tumour control. Starr and Zimmerman observed that there was a 26 times greater likelihood of orbital recurrence with extrascleral extension than without.[1] Orbital recurrence was six times more likely to occur if the tumour nodule was non-encapsulated or surgically transected than if it was encapsulated, and 50% of tumours without a capsule or apparently transected will recur in the orbit.[1]

There may not be an independent adverse effect of extrascleral extension on survival rate. Starr and Zimmerman found that local extraocular spread reduces the five-year survival rate from 67% without this finding to 34% with,[1] but in a multivariate analysis Kidd and coworkers were unable to demonstrate a significant independent adverse effect of extrascleral extension of melanoma on the prognosis for survival.[9] Starr and Zimmerman had already demonstrated that there was a significantly greater number of melanomas of more malignant cell type among patients with extrascleral extension than among those without,[1] and this feature of tumours which extend out of the eye locally may account for the increased mortality with which they are associated.

There are no data from multivariate analysis to establish whether the development of orbital recurrence has an independent adverse effect on survival rate. However, the five-year survival rate has been found to be reduced from 34% for all patients with extrascleral extension to 11% for those who subsequently have a recurrence in the orbit,[1] and there would seem to be strong grounds for attempting to prevent the development of orbital recurrence by adjuvant orbital radiotherapy.

The primary aim of any treatment proposed for extrascleral extension of choroidal malignant melanoma is therefore to intercept and remove or destroy any malignant cells which may be in transit through the orbit to distant sites and thereby to prevent metastasis if this has not already taken place. A subsidiary aim is to prevent orbital recurrence and to limit the chance of this in turn leading to metastatic death. The optimal method for achieving these ends is controversial, as are the relative benefits to the patient, but the recommended approach now depends largely on the extent of the extraocular element of the tumour.

Orbital exenteration has been the standard treatment for extrascleral extension in many centres, and its role continues under discussion. Although Rendahl maintained that exenteration was never indicated for extrascleral extension of melanoma because it did not improve the outlook for survival,[7] Shammas and Blodi reported a high five-year survival rate following the operation and considered that the procedure may be curative if performed early.[3] More recently, however, Kersten, with Blodi and others, observed that after extended follow-up the tumour-associated mortality rate approached that of patients refusing exenteration.[10] Only in cases with non-encapsulated or surgically transected extension did exenteration appear to increase survival. Earlier Starr and Zimmerman had been unable to find evidence that exenteration improved the survival chances of patients with extrascleral extension but recommended increased use of the operation on the grounds that it reduced the likelihood of orbital recurrence and that it was associated with prolonged survival in anecdotal cases.[1]

Although exenteration has a good record in preventing orbital recurrence, Affeldt and coworkers have pointed out that the procedure is infrequently used because of the cosmetic deficit.[6] While adverse cosmetic factors have probably been overstated, lingering doubts about the value of exenteration in improving survival rate have led to consideration of alternative approaches, particularly for minor degrees of extrascleral extension. Enucleation alone[8 11] or followed by radiotherapy[6 8 11 12] has been recommended for episcleral extension and enucleation plus either tenonectomy or radiotherapy for a well encapsulated extrascleral extension,[12] with exenteration reserved for a non-encapsulated or surgically transected nodule.[7] In this centre surgical transection seen only on histopathological examination has not been considered an indication for exenteration, a procedure which has been reserved for individuals with intraoperative evidence of residual orbital melanoma. The rationale for this approach has been that, while radiotherapy is unlikely to achieve sustained local control of bulk disease, it has a good chance of destroying a few cells which may have been left behind in the orbit at operation.

Radiotherapy has not achieved wide acclaim as a treatment of extrascleral extension, mainly because malignant melanoma is a relatively radioresistant tumour.[13] Nevertheless, sustained tumour regression has been reported by several authors following irradiation of small intraocular melanomas.[14-17] Only Lommatzsch and Dietrich[18] and Sobanski and Zeydler[19] have reported on series in which the orbit has been irradiated after enucleation. Both claim significantly better survival than with enucleation alone. They suggest that postenucleation irradiation damages or destroys tumour cells which may be scattered into the surrounding tissues during the operation to remove the eye, though neither author has presented data on the comparative orbital recurrence rates with and without radiation to support this view.

### SURVIVAL

The five-year survival rate of 51% for patients in the present series compares favourably with the figure of only 34% alive at five years in Starr and Zimmerman's group of patients with extrascleral extension of uveal melanoma.[1] However, no direct comparisons can be made between the two groups which are not matched for factors such as tumour size and cell type. Eleven out of the 17 study patients died of melanoma metastases, though 10 did not develop orbital recurrence.

### ORBITAL RECURRENCE

At only 6% the orbital recurrence rate in the present series is significantly lower than the 18% reported after extrascleral extension by Starr and Zimmerman,[1] though, once again, direct comparisons cannot be made because the two groups of patients are not matched. In fact 70% of the patients in the present series had non-encapsulated or surgically transected melanomas, whereas only 25% of Starr and Zimmerman's patients had this potentially more serious degree of extrasclera spread. Melanoma may recur in the orbit 20 years or more after enucleation,[8 20 21] and the incidence of recurrence is unlikely to be fully ascertained without an extremely long period of follow-up. However, both the present series and that of Starr and Zimmerman were followed up for a minimum of five years. The use of radiotherapy after extrascleral extension is not discussed in Starr and

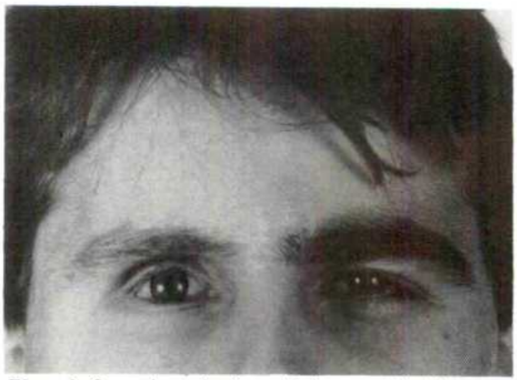

*Figure 3: Cosmetic result after radiotherapy with right eye prosthesis in situ. The right eyebrow hair loss is more marked in this patient than is usual.*

Zimmerman's article, though that is not to say that it was not given in some of their patients.

Modern orbital radiotherapy produces very little cosmetic deficit (Fig 3). This is restricted to slight loss of brow hair and thinning of the eyelashes. With adequate fractionation there is very little loss of soft tissue, and tear production is maintained, so that the prosthesis is not dry. Patients receiving radiotherapy can still receive an acrylic orbital implant integrated with the extraocular muscles for realistic movement of the artificial eye. The present study does not produce conclusive evidence of better survival or a reduced orbital recurrence rate when radiotherapy is given after enucleation of an eye with extrascleral extension. A prospective randomised study would be required to settle this issue. Meanwhile the morbidity from orbital radiotherapy is so slight that adjuvant treatment is advised in all cases when extrascleral extension is detected after enucleation for a posterior melanoma except when there is an extensive bulk of residual orbital tumour, when orbital exenteration remains the treatment of choice.

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# Topical fluconazole for experimental candida keratitis in rabbits

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**Abstract**

**Using a reproducible model of *Candida albicans* keratitis in rabbits we studied the effect of topical fluconazole, a new triazole. *Candida albicans* DSM 70010 (2·5×10$^5$ cells) was injected into the corneal stroma of both eyes of 21 rabbits. All eyes developed a corneal ulcer. Forty-eight hours after inoculation the animals were divided into three groups: (1) 14 eyes, received fluconazole (2 mg/ml) and the epithelium subsequently removed; (2) 14 eyes, received only fluconazole drops; (3) 14 eyes, received 0·9% NaCl: half of this group was also debrided. We applied one drop of either substance 10 times a day for 24 days. A further six rabbits were used to judge if the drug penetrated into the cornea and aqueous humour. There was a highly significant difference between the fluconazole groups (1, 2) and the control group (3) as to hypopyon and complications (descemetocele, corneal perforation) as well as recultivation of *C. albicans* from corneal tissue. The difference between the fluconazole groups with and without debridement was not significant. The drug penetrated into the cornea and aqueous humour of both uninflamed and inflamed eyes.**

Fungal infections of the cornea have markedly increased during the last decades.[1,2] Apart from polyenes such as amphotericin-B, nystatin, and pimaricin (natamycin), azoles such as the imidazoles and ketoconazole have been applied to fungal keratitis. The azoles proved effective and were non-toxic to the eye.[3,4] However, the treatment of clinical keratomycoses is still inefficient.[5,6]

Fluconazole (2-(2,4,-difluorophenyl)-1,3-bis (1 H-1,2,4-triazol-1-yl) propan-2-ol; UK 49·858) is a new triazole compound (molecular weight 306·3) which has certain properties suggesting its use for the treatment of fungal keratitis. It has been reported to be more efficient than ketoconazole in systemic candidosis of immunosuppressed as well as normal mice.[7,8] Moreover, fluconazole is the only antifungal azole derivative which penetrates into the cerebrospinal fluid.[9,10] Parenterally administered fluconazole under experimental conditions was shown to penetrate freely into ocular tissues.[11]

This is the first report on the use of topical fluconazole in experimental *Candida albicans* keratitis in rabbits. We also studied penetration of the drug into the cornea and aqueous humour.

## Material and methods

*Bioavailability.* One drop of aqueous fluconazole solution (2 mg/ml) was applied to both eyes of six rabbits every hour for a period of eight hours. On three animals the corneal epithelium had been gently removed with a hockey knife under a microscope. Fifty minutes after the last treatment the eye was irrigated with saline.

Aqueous humour samples (0·2 to 0·3 ml) were obtained by puncture of the anterior chamber with a 26 gauge needle. Corneal samples were excised at the limbus with scissors and ground in a tissue grinder (Ultra-Turrax, Janke and Kunkel, Stauffen, Germany). These samples were centrifuged at 12 000 rpm.

Serial dilution tests of both the aqueous humour samples and the supernatant of the corneal samples were performed on microplates. A 100 µl candida suspension (10$^3$ blastoconidia/ml) from a 24 h culture in glucose peptone broth containing 50 µg/ml gentamicin sulphate was added to 50 µl of the samples. The plates were incubated for 24 hours at 37°C. The minimal inhibition concentration (MIC) of fluconazole was determined by serial dilution under comparable conditions.

*Inoculum.* We used *Candida albicans* DSM (German Collection of Micro-organisms) No 70010, which shows filamentous growth in aqueous humour.[12] Yeast cells from a 24 h culture in Sabouraud agar were suspended in peptone broth, counted with a haemacytometer, and adjusted to a concentration of 2·5×10$^{10}$ cells/l.

*Animals.* Twenty-one male, pigmented, inbred rabbits, weighing approximately 2·5 kg each were used. No pretreatment was performed.

*Inoculum procedure.* This method has been described previously.[13] The animals were anaesthetised with intramuscular xylazin and ketamine, 5 mg/kg body weight. To avoid preservatives no local anaesthetic was applied. Under an operating microscope a 27 gauge needle was inserted into the central corneal stroma to a depth of about one-half of the corneal thickness. A 10 µl inoculum, containing 2·5×10$^5$ cells, was injected in both eyes. No reflux of the inoculum was observed. If penetration into the anterior chamber occurred, the animal was removed from the study.

*Therapy.* Forty-eight hours after inoculation the animals were randomised into three groups (14 eyes of 7 animals each). In groups 1 and 2 aqueous fluconazole solution (2 mg/ml in 0·9% NaCl) and in group 3 0·9% NaCl was administered. In addition, the epithelium of the eyes in group 1 was gently removed. To exclude any mechanical effect of debridement the same was done in half of those in the control group 3. This procedure was done every third day with a hockey knife under a microscope. All eyes received a daily treatment of 0·5% aqueous gentamicin sulphate (without preservatives) to avoid a bacterial infection.

*Evaluation of ocular infections.* All eyes were examined every day and a standardised photographic record was made. The occurrence of a descemetocele, corneal perforation, and hypopyon was noted.

*Fungal recultivation.* After 24 days the animals were killed by intravenous thiopentone sulphate. Aqueous humour samples were obtained from all eyes to study the penetration of fluconazole into inflamed eyes. Serial dilution tests for antifungal activity were performed as described above. The cornea was excised at the limbus and divided through the centre of the ulcer. The cut surfaces of both sections were pressed on to Sabouraud agar containing 50 µg/g gentamicin sulphate and the plates incubated for one week at 21°C. Positive cultures were plated on blood agar and incubated for 48 hours at 37°C for further differentiation. These cultures were subjected to an auxanogram[14] (API-20-C) to establish the presence of *C. albicans*.

## Results

*Bioavailability.* Penetration of fluconazole into the cornea and aqueous humour of uninflamed eyes is shown in Table I. There is a moderate difference between eyes with and without corneal epithelium. In inflamed eyes (24 days after infection) the results of aqueous humour samples are the same as in non-inflamed eyes.

*Course of infection and complications.* All 42 eyes inoculated with *Candida albicans* DSM 70010 developed corneal infiltrates on day 2 with an average size of 3×3 mm. These infiltrates progressed to an ulcer between days 5 and 8. The incidence of hypopyon and complications (descemetocele or corneal perforation) is shown in Table II for each group. There was a marked difference between the therapy groups (1 and 2) and the control group (3a and 3b) in the occurrence of descemetoceles or perforations ($p<0{\cdot}01$; $\chi^2$ test). Figures 1–4 show typical corneal infections of each group on day 21.

The drug was well tolerated by all animals. No adverse effect could be observed.

*Recultivation.* Table III lists the results of *Candida albicans* recultivation. In group 1 no viable yeasts were recovered. In group 2, two of 14 samples showed candida growth. These results are highly significant compared with that of group 3a+b ($p<0{\cdot}01$; $\chi^2$ test).

TABLE I *Penetration of fluconazole into the rabbit cornea and aqueous humour of uninflamed eyes. Growth of* C. albicans *was inhibited by the indicated dilutions of cornea, homogenate or aqueous humour*

| | *With debridement* | *Without debridement* |
|---|---|---|
| Corneal homogenate | 1:4 | 1:2 |
| Aqueous humour | 1:8 | 1:2 |

TABLE II *Influence of topical fluconazole on hypopyon, descemetocele, or perforation in experimental candida keratitis*

| | *Eyes* | *Hypopyon* | *Descemetocele or perforation* |
|---|---|---|---|
| Group 1 (fluconazole+debridement) | 14 | 3 | 0 |
| Group 2 (fluconazole without debridement) | 14 | 6 | 1 |
| Group 3a (0·9% NaCl+debridement) | 6 | 6 | 5 |
| Group 3b (0·9% NaCl without debridement) | 8 | 7 | 8 |

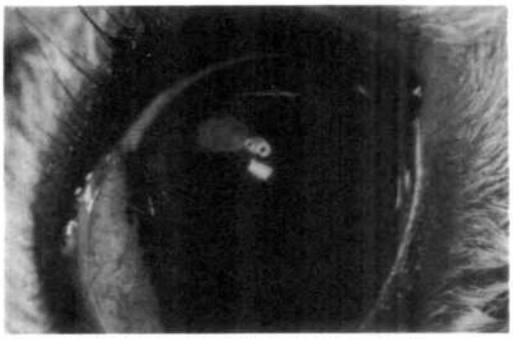

*Figure 1: Candida keratitis of group 1 (fluconazole+debridement) on day 21.*

## Discussion

Most antifungal drugs are effective against superficial mycoses but are less successful in counteracting deep mycotic infiltrations. In particular, the treatment of keratomycosis is often frustrating owing to limited tissue penetration, narrow antimicrobial spectrum, and toxicity of the antifungal agents currently available.

The new triazole antifungal fluconazole, by virtue of its pharmacological properties, offers a fresh opportunity for the topical treatment of keratomycosis. The drug acts against all pathogenic *Candida* species except *C. krusei*[15] and hence encompasses the majority of fungi which are notorious as causative agents of keratomycosis.[16-18] Fluconazole is exceptionally hydrophilic, which is reflected by low protein binding and high penetration into cerebrospinal fluid, as well as by intestinal absorption and renal excretion.[15 19 20] In rabbits fluconazole was shown to reach ocular tissues after intravenous administration.[11] In addition fluconazole was shown to be non-mutagenic and less toxic than the other azoles.[19]

In the present study we used a rabbit model to investigate the potential of fluconazole in the therapy of deep keratitis due to *C. albicans*. The model is reproducible without the need of immunosuppressive pretreatment.[13] Therapy is

TABLE III *Recultivation of* Candida albicans *DSM 70010 after 24 days of treatment with topical fluconazole*

| | *Eyes* | *Positive* |
|---|---|---|
| Group 1 (fluconazole+debridement) | 14 | 0 |
| Group 2 (fluconazole without debridement) | 14 | 2 |
| Group 3a (0·9% NaCl+debridement) | 6 | 5 |
| Group 3b (0·9% NaCl without debridement) | 8 | 7 |

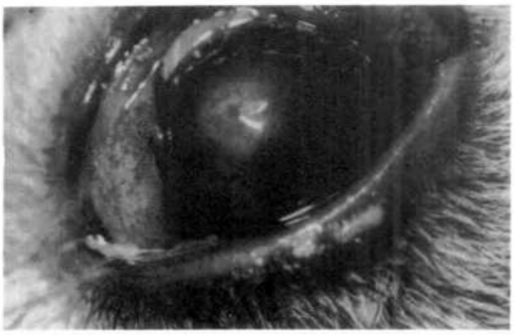

*Figure 2: Candida keratitis of group 2 (fluconazole without debridement) on day 21.*

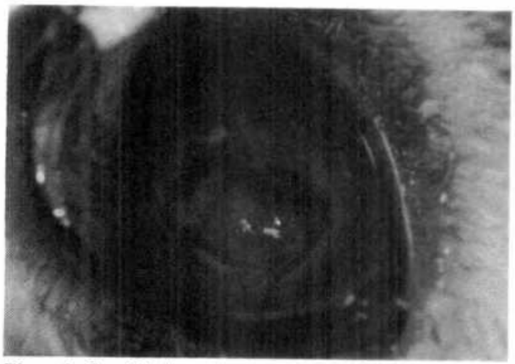

*Figure 3: Candida keratitis of group 3a (0·9% NaCl+ debridement) on day 21.*

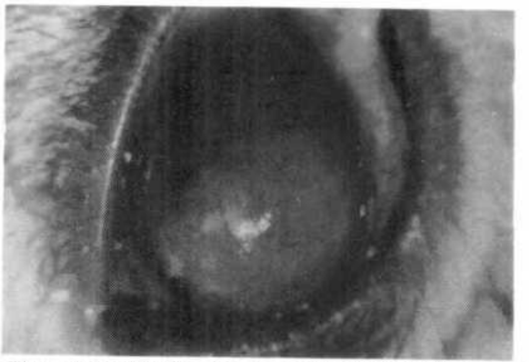

*Figure 4: Candida keratitis of group 3b (0·9% NaCl without debridement) on day 21.*

started only on day 2, when stromal keratitis is manifest; hence the model more closely parallels human corneal candidiasis than a regimen which begins treatment one hour after infection.[21]

Our results demonstrate the efficacy of fluconazole in the topical therapy of experimental candida keratitis. As to complications such as descemetocele and corneal perforation, there was a highly significant difference between the treated eyes and the controls. The beneficial effect was confirmed because almost no recultivation of *C. albicans* was possible after 24 days of treatment.

However, no significant difference between the debridement and no-debridement groups was found. This finding contrasts with results from similar experiments using amphotericin B, which revealed a highly significant difference in favour of debrided eyes.[22] The effect of debridement on the penetration of amphotericin B reflects its higher molecular weight (924·11), since the limiting size of molecules for diffusing into the normal cornea is about 500·00.[23]

We conclude that fluconazole proved highly effective in the therapy of experimental candida keratitis. If debridement of the corneal epithelium is undesirable, this drug seems to be superior even to amphotericin B.[22]

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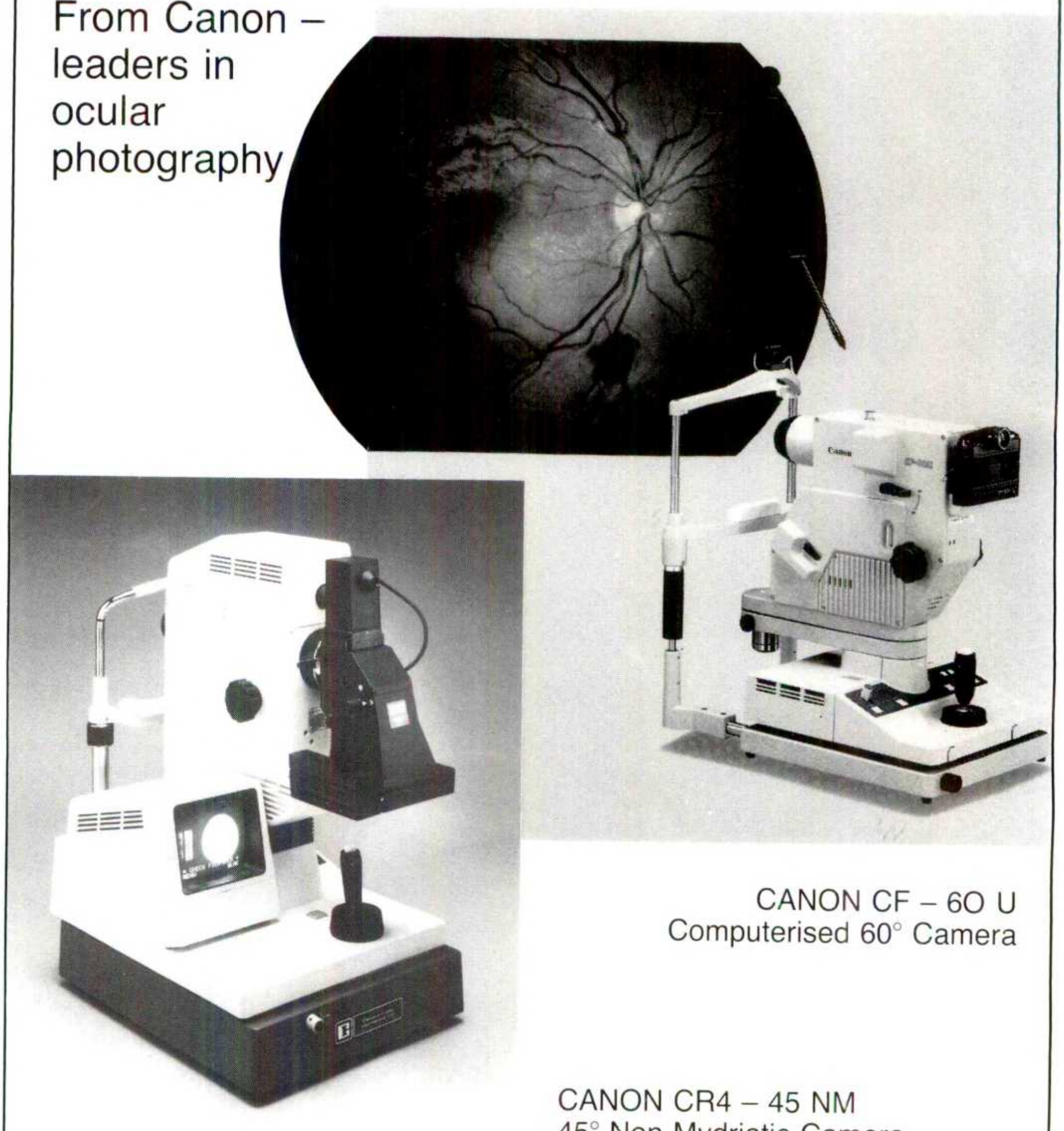

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# Magnetic resonance imaging of juxtapapillary plaques in cadaver eyes*

David F Williams, William F Mieler, Glenn J Jaffe, Dennis M Robertson, Lloyd Hendrix

## Abstract

**Adequate treatment of juxtapapillary melanomas with episcleral plaque brachytherapy using lower energy radiation sources may be difficult because of uncertainties regarding the relationship of the plaque to the optic nerve and tumour base. We obtained magnetic resonance images of a dummy plaque placed in a juxtapapillary location in cadaver specimens. Although it is possible to place a plaque in close association with the optic nerve sheath, a tissue barrier exists which may prevent actual contact between the plaque and nerve. Posterior tilting of the plaque may also occur. Because of these uncertainties regarding plaque placement, juxtapapillary melanomas should be considered a distinct subgroup when evaluating the efficacy of radioactive plaque brachytherapy in the treatment of choroidal melanoma.**

Juxtapapillary melanomas (those extending within 3 mm of the optic nerve head) constitute approximately 3 to 33% of tumours in reported series of radiation treated choroidal melanomas.[1-3] When giving radioactive plaque therapy in the treatment of juxtapapillary choroidal melanomas several problems are encountered that are not seen in the treatment of more peripherally located tumours. First, the diameter of the optic nerve sheath is 1·5 to 2·5 mm larger than the optic disc.[4] Thus when treating a tumour in apposition with the disc it is not possible to place a plaque fully round the base of the tumour. Secondly, it is not clearly known how close to the optic nerve sheath it is possible to place a plaque owing to uncertainties in the posterior anatomy. Thirdly, tilting of the plaque away from the globe may create further uncertainty in the plaque relationship to the optic nerve and the adjacent sclera, such that accurate estimates of radiation delivered to the tumour and/or optic nerve may not be possible. Because of these uncertainties in plaque placement, the ability adequately to treat tumours whose posterior border is within 2 to 3 mm of the optic nerve head may be questioned.

We used magnetic resonance imaging to investigate the relationship of a plaque to the optic nerve in six fresh unembalmed cadaver specimens 12–72 hours post mortem. The purpose of this study was to evaluate the placement of a plaque with regard to the optic nerve sheath in the different quadrants of the globe, and to establish whether tilting of the plaque away from the sclera may occur, or other positioning problems as well.

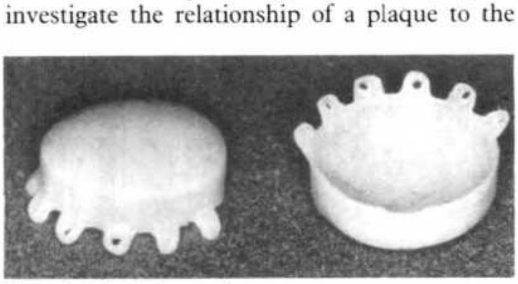

*Figure 1: Plastic dummy plaque.*

## Material and methods

A plastic dummy plaque, identical in design to the Collaborative Ocular Melanoma Study (COMS) plaque[5] measuring 14 mm in diameter with a 2·6 mm circumferential lip was used (Fig 1). The plaque was placed in a juxtapapillary location in all four quadrants of the globe in six eyes from fresh cadaver specimens. After the conjunctiva and Tenon's capsule had been incised, the plaque was placed on the scleral surface. The globe was rotated away from the desired quadrant by rectus muscle sutures, and the plaque was slid on the scleral surface between the recti muscles as far posteriorly as possible. When significant resistance to further movement was encountered, and when the entire globe moved with further attempts at posterior positioning, apposition to the optic nerve sheath was presumed and manipulation was stopped. The globe was then rotated back to the primary position while mild posteriorly oriented pressure was maintained on the plaque to prevent plaque movement. In all instances the anterior position of the plaque could be directly observed and was noted to be in apposition to the sclera; therefore the plaque was not sutured to the sclera. The conjunctiva and Tenon's capsule were then reapproximated loosely to the limbus.

Magnetic resonance images were obtained

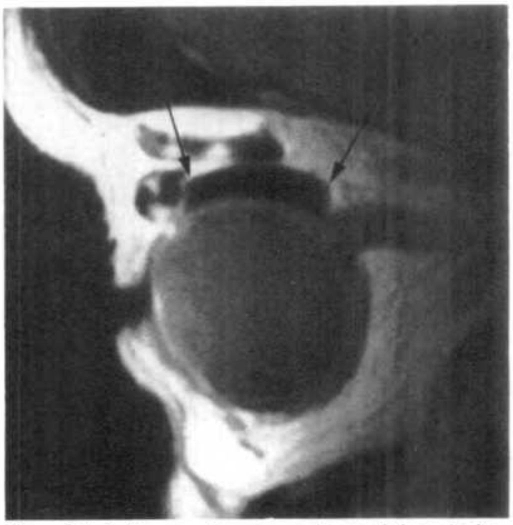

*Figure 2A: Left, magnetic resonance image of plaque in the superonasal quadrant (arrows).*

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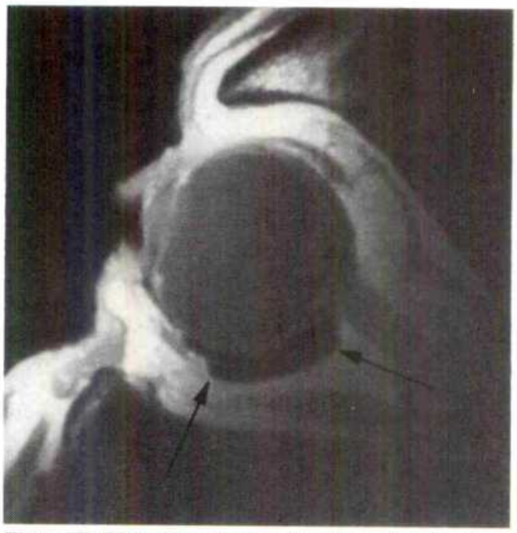

*Figure 2B: Right, plaque in the inferotemporal quadrant (arrows.)*

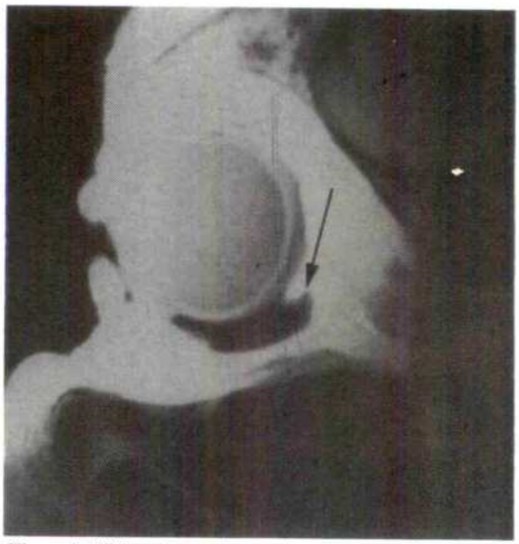

*Figure 4: Tilting of posterior portion of plaque away from the sclera (arrow).*

with a General Electric Sigma system operating at 1·5 tesla. A 2-inch (5-cm) diameter counter-rotating current surface coil[6] (Medical Advances, Inc, Wauwatosa, WI) was used as a local radio frequency receiver and the body coil as a transmitter. Axial, sagittal, and oblique T1 weighted images ($T_R=600$ ms, $T_E=20$ ms) were obtained. Additional parameters included slice thickness of 3 mm with a gap of 1 mm, 8 cm field of view, 256×128 matrix, and two excitations. Acquisition time averaged 4 minutes for a series of eight images. The plaque, which contains no mobile protons, emits no signal and therefore appears black in contrast to the surrounding soft tissues.

## Results

We obtained images showing the plaque relationship to the optic nerve in the four quadrants of the globe. A total of six eyes were scanned. The plaque could be placed in close association with the optic nerve sheath in all four quadrants. A close approach to the optic nerve sheath was easily obtained superonasally and inferonasally (Figs 2A, B) while the inferotemporal approach required slightly more manipulation and the superotemporal approach was the most difficult.

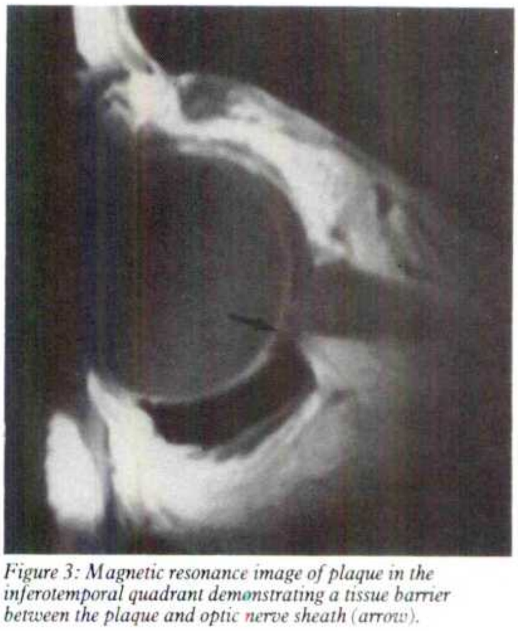

*Figure 3: Magnetic resonance image of plaque in the inferotemporal quadrant demonstrating a tissue barrier between the plaque and optic nerve sheath (arrow).*

In several scans in which the plaque was thought to be in apposition to the optic nerve the scan showed tissue between the plaque and the optic nerve (Fig 3).

Additional difficulties encountered in plaque placement were tilting of the posterior portion of the plaque away from the optic nerve and sclera (Fig 4), and posterior positioning of the plaque along the optic nerve sheath (Fig 5). These findings each occurred in one of six eyes scanned with plaque placement in the inferior quadrants.

## Discussion

The rationale for the treatment of ocular melanoma with radioactive plaque brachytherapy is the delivery of an amount of radiation adequate to induce regression of the tumour while minimising radiation scatter to adjacent ocular tissues, thus preserving visual function. Optimal treatment of the tumour requires that the radiation field fully encompass all borders of the tumour. The use of high energy radiation sources, such as cobalt-60, results in significant scatter of radiation from which it is not possible adequately to shield adjacent tissues. This scattered radiation may minimise undertreatment of

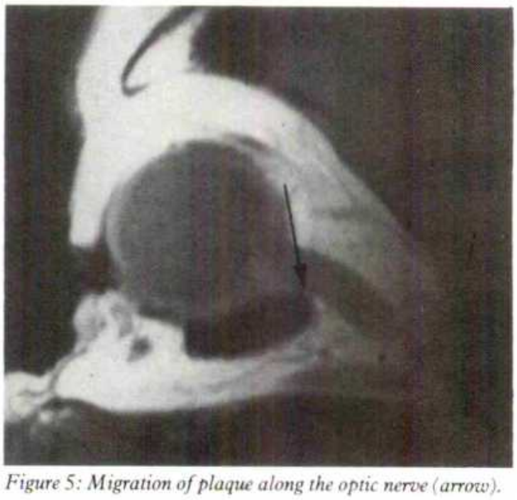

*Figure 5: Migration of plaque along the optic nerve (arrow).*

tumour margins when a plaque is not accurately placed over the tumour base but may also result in excessive radiation damage to normal ocular tissues. Radiation scatter may be minimised by utilising $\beta$ emitters or low energy $\gamma$ emitters, such as ruthenium-106 or iodine-125, and by providing a circumferential lip on the plaque to shield adjacent tissues.[1,7-9]

Brachytherapy treatment of juxtapapillary melanomas with low energy radiation sources presents special difficulties because of uncertainties in the posterior anatomy with regard to plaque placement. It is known that the optic nerve within the scleral canal is approximately 1.5 mm in diameter while the optic nerve sheath is 3–4 mm in diameter.[4] Thus, even if a plaque were placed in apposition to the optic nerve it may not be possible fully to cover the base of a tumour with a margin extending closer than 0·75 to 1·25 mm from the optic nerve head. If the plaque is not placed in apposition to the optic nerve sheath, the potential for adequate treatment of a juxtapapillary melanoma would diminish accordingly. Echography has been used to verify radioactive plaque positioning in the treatment of choroidal melanoma.[10,11] The assessment of the position of the plaque with regard to the optic nerve is quite difficult, however, owing to the acoustic shadowing caused by the strong reflectance of the metallic plaque.

Using magnetic resonance imaging, we have obtained clear images and have shown that it is possible to place a plaque in close association with the optic nerve sheath. However, an anatomical barrier does exist which may prevent actual contact between the plaque edge and the optic nerve (Fig 2). Although the resolution obtained is insufficient precisely to identify the small anatomical structures, it is likely that the penetration of the short posterior ciliary arteries and nerves circumferential to the optic nerve provide at least part of the anatomical barrier between the plaque and nerve.

We also found that more manipulation was required to place the plaque adjacent to the optic nerve in the temporal quadrants than in the nasal quadrants. Potential anatomical factors making the temporal approach to the optic nerve more difficult include the insertion of the inferior oblique muscle and the greater distance from the temporal limbus to the optic nerve.

Another difficulty which may be encountered is tilting of the plaque away from the sclera. Because of the relative inaccessibility of the point of insertion of the optic nerve into the sclera, direct observation of the most posterior portion of the plaque may not be possible, and posterior tilting of the plaque may occur unknown to the surgeon. The radiation source would thus be displaced away from the tumour apex and directed towards the optic nerve, with resultant under treatment of the tumour and excessive radiation scatter to the nerve.

There are several potential complicating factors in this study. (1) We used unembalmed cadaver specimens which were 12 to 72 hours old. The effect of postmortem tissue changes on ease of plaque placement and the ability to obtain apposition to the optic nerve are unknown. (2) All scans were obtained with the specimen in the supine position. The effect of different body positions or ocular movements on plaque-nerve orientation are unknown. (3) Our dummy plaque was made from lightweight plastic. A heavier metallic plaque with radioactive seeds may result in changes in plaque-nerve orientation, particularly with patient movement. (4) The circumferential lip on the dummy plaque was 2·6 mm. It is possible that, if the lip was smaller, thus producing a 'flatter' plaque, there would be less tissue distortion and less resistance to posterior placement of the plaque. This smaller lip would result in less shielding of scatter radiation, however. In a similar fashion, a notched plaque could be utilised, though there is still potential for tissue distortion and it may not be possible to place the plaque in true apposition with the optic nerve sheath. (5) the rectus and oblique muscles were not detached, and the ease of application of a plaque directly under the muscles is not fully known. Though posterior visualisation would be enhanced with muscle removal, direct assessment of the optic nerve sheath remains exceedingly difficult. And, finally (6), technical difficulties involving image acquisition on the magnetic resonance scanner in an oblique plane may significantly affect image quality and acquisition time. It is expected that as advances in software occur, oblique images will become easier to obtain and the images will be of improved quality.

In summary, low energy brachytherapy treatment of a juxtapapillary melanoma may be inadequate for several reasons. The normal anatomical relationship of the optic nerve sheath to the optic nerve head places a limit on how close a tumour margin can be to the optic nerve head and still be potentially covered by an episcleral plaque. A tissue barrier between the plaque rim and optic nerve sheath, as described above, may increase the difficulty of fully treating tumour margins. Tilting of the plaque may also occur, resulting in inadequate radiation delivery to the tumour apex while delivering excessive radiation scatter to the optic nerve.

Though magnetic resonance imaging cannot be readily used with metallic plaques in patients, this study demonstrates that the juxtapapillary placement of plaques may be much less precise than previously realised. These uncertainties indicate that juxtapapillary tumours should be considered as a distinct subgroup meriting separate analysis of the efficacy of treatment.

This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc, and by National Institutes of Health grant AR 33667.

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*British Journal of Ophthalmology*, 1990, 74: 47–48

## MINI REVIEW

# Aetiology of myopia

Although clinicians are preoccupied with treating myopia and its complications, the causation is worth our attention, and particularly the results of experiments on animals in recent years. These have some implications for the treatment of patients.

Myopia's remarkable bilateral symmetry suggests a hereditary basis. This is supported by Sorsby's observation[1] that 78 pairs of identical twins showed close agreement in their refractions, whereas 40 pairs of non identical twins showed little more agreement than control pairs of siblings. Some families show a dominant hereditary pattern,[2] some a recessive,[3] and perhaps some an X-linked,[4] but probably most cases are multifactorial,[2] including environmental factors.

We would need no statistical evidence that glaucoma at birth or in early life often produces myopia because of a large eyeball. Is axial myopia in general the result of a slightly raised intraocular pressure in the early growing years?[5-8] Not proven, because the higher ocular tension associated with myopia may result from the myopic process rather than cause it.

Hubel and Wiesel won a Nobel prize for their work on experimental amblyopia in kittens subjected to unilateral tarsorrhaphy. The up-market application of this work to young rhesus macaque *(Macaca mulatta)* and stump-tailed macaque *(M. arctoides)* monkeys produced a quite fascinating result: the eyes on the side subjected to tarsorrhaphy were almost all axially myopic, with the familiar fundus changes.[9] (Such work usually attracts the description 'serendipitous'. There is a great need for a complementary word which describes much research – great and serious effort, with much diligent reading of the literature and painstaking experiments – resulting in very small discoveries.) Corneal opacities caused by injection of a fine suspension of polystyrene beads produced the same effect as lid fusion.[10] Two young rhesus monkeys with unilateral lid fusion which were raised in the dark failed to show myopia.[11] Accordingly, unfocused light is a prime mover in producing this experimental myopia, not a mechanical or thermal effect of lid fusion.

Is there a human counterpart? The eyes of children with unilateral ptosis are more myopic or less hypermetropic on the affected side than on the other.[12] Cataracts in early life are also factors in causing abnormal elongation of the eyeball.[13-15]

Does optic nerve section prevent lid fusion myopia? Three rhesus monkeys developed the usual myopia in spite of 'intracranial section of the optic chiasm'.[11,16] It is sometimes facile, however, to transfer observations in one species to another: the same procedure in one *M. arctoides* monkey did prevent lid fusion myopia.

Bilateral lid fusion produces bilateral axial myopia in monkeys.[9] Removal of the striate cortex has no effect.[16] Topical atropine (and removal of the ciliary ganglion) also had no effect in rhesus monkeys, but did prevent lid suture myopia in four *M. arctoides* animals, which suggests that accommodation is a factor in the latter species. A pharmacological blocker of acetylcholinesterase, isofluorophate, which produces excessive accommodation, had no effect on the experimental myopia in rhesus and stump-tailed monkeys.[16] Sympathetic denervation and trigeminal section also failed to alter progression of this myopia.

The effect of these experiments is localised to the tarsorrhaphised eye, provided the animals are young. Surely the retina must be the source of the stimulus to the sclera? What chemical substance diffuses from the retina to affect the sclera? How can the substance manage to avoid being washed away by the fast flowing choroidal circulation? Is the rate of formation of cross linkages in scleral collagen reduced?

A surgence of interest in growth factors in recent years may be relevant.[17-20] Indeed, the retina may not be the passive victim of scleral growth, but may conceivably be the author of its own destruction.[21,22]

The latest instalment to this whodunnit is even more difficult to explain. Chickens,[23-25] like tree shrews,[26,27] also suffer from deprivation myopia. Several groups of chicks were subjected to deprivation of localised areas of retina.[28] In some, the 'nasal' (anterior) retina was deprived of patterned images by a white translucent occluder with a window anteriorly which allowed normal images on temporal (posterior) retina. In others the window in the occluder was positioned posteriorly to allow focused images on nasal (anterior) retina, leaving the temporal (posterior) retina deprived. Consistently, the half of the eyeball receiving unfocused light was axially longer and (more) myopic than the half receiving focused images. Are there human counterparts? Can we find here an explanation for localised staphylomata in human myopic eyes? Can we find patients with corneal or lens opacities from childhood restricted to one area and investigate with B-scan ultrasound whether the appropriate side of the eyeball is 'myopic'?

Are there any practical implications for the management of myopia in all this? We are already having to make up our minds on whether and in what circumstances to advise spectacles, contact lenses, radial keratotomy, Fukala's operation, insertion of an anterior chamber intraocular lens in the phakic eye, removal of the clear lens with or without insertion of an IOL, epikeratophakia, and the computer controlled regrinding of the air-cornea interface. We are all well aware of the importance of choosing our parents – but genetic engineering is beginning to mitigate the genetic imperative. Should we deprive our growing children of the comfort of a night light? Should they be punished for reading by torchlight under the bed clothes? Maybe the Japanese and Chinese will be the first to abandon their print in favour of audio texts, not just in waking hours but subliminally during sleep. There are other reasons to make us try to minimise the severity of corneal and lens opacities, and the duration of occlusion. Few of us would feel justified in prescribing bilateral atropine drops to children for months or years.[29-33] There is good evidence in a reasonably well controlled but unfortunately only single-masked study that bifocals reduce the rate of progression of myopia in children.[34] Multifocals would probably be more acceptable.

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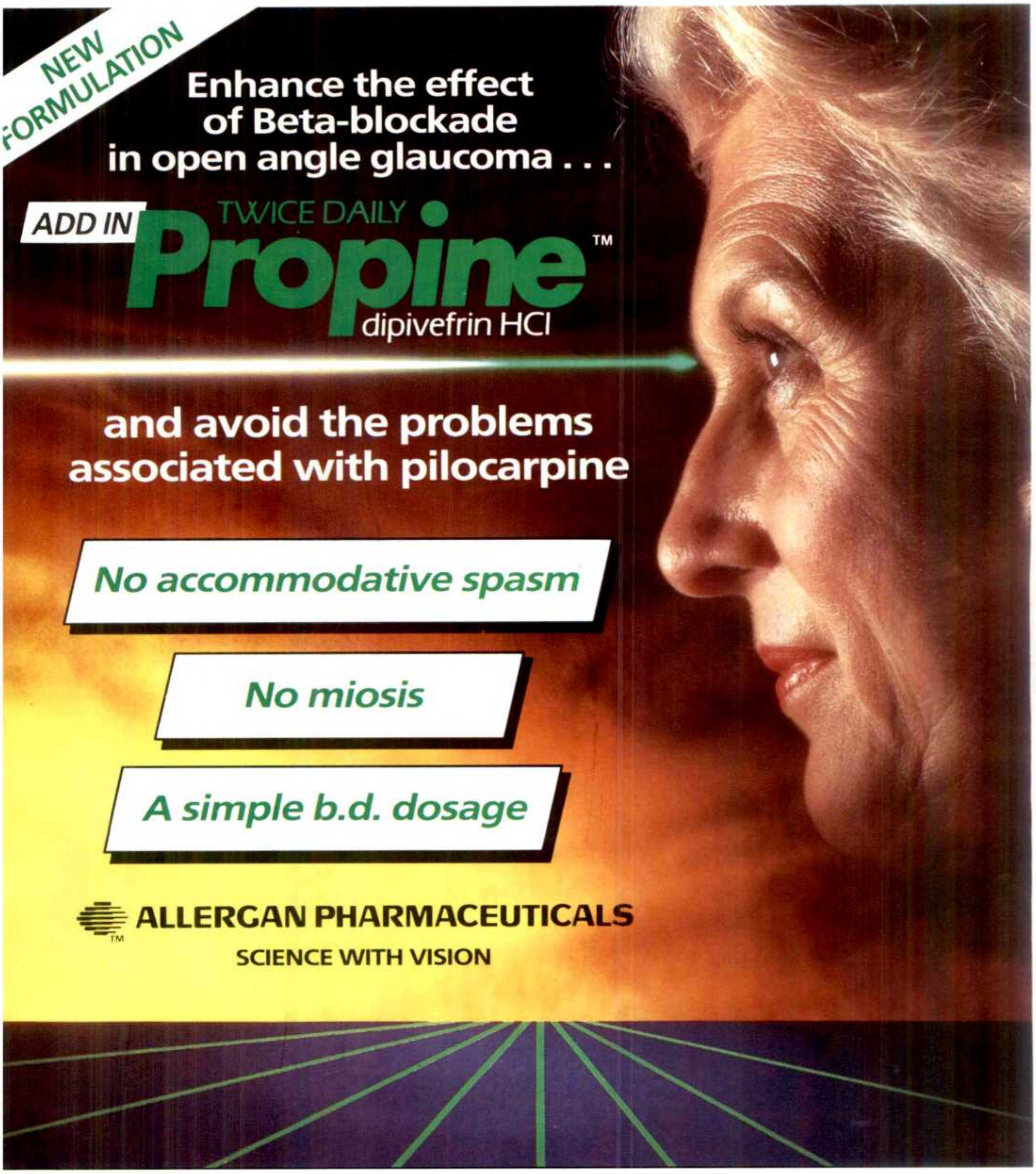

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*British Journal of Ophthalmology*, 1990, **74**: 49–51

## CASE REPORTS

# Retinal dysfunction as an initial ophthalmic sign in AIDS

Scott E Brodie, Alan H Friedman

**Abstract**

**Three cases of patients with AIDS in whom severe retinal dysfunction preceded the development of widespread funduscopic abnormalities are presented. The disparity between the minimal extent of visible retinal lesions and the severe loss of retinal function was confirmed by visual field and electroretinographic studies. This pattern of early visual loss in AIDS patients may represent infection of the retina by the HIV virus.**

Previous descriptions of retinopathies associated with AIDS, such as cytomegalovirus, herpes simplex virus, and toxoplasmosis, have emphasised their ophthalmoscopic and histopathological manifestations.[1] We report here on three patients in whom visual loss and electroretinographic (ERG) abnormalities preceded the development of visible exudative or haemorrhagic lesions of the retina and pigment epithelium. In one patient visual loss was the initial presenting symptom of AIDS.

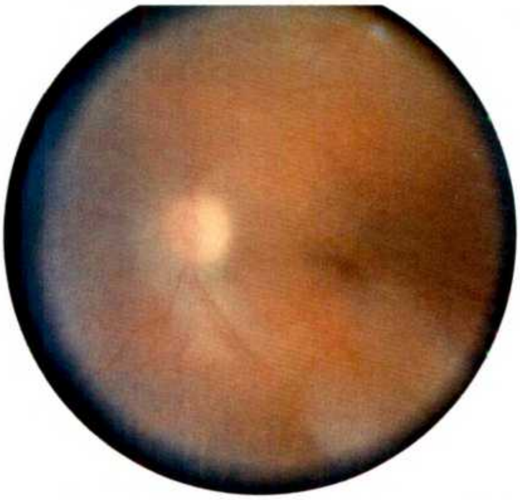

*Figure 1: Fundus photograph of left eye of patient 1, showing vitreous haze without abnormalities of the retinal architecture.*

CASE 1

A homosexual male aged 28 presented with a three-month history of progressive loss of vision in both eyes. A concurrent history of fatigue, weight loss, intermittent diarrhoea, and generalised lymphadenopathy was noted. Visual acuity fell to light perception in the right eye, and barely light perception in the left eye. Examination of the anterior segments gave normal results, but a diffuse vitritis without clumps or skeins was seen in both eyes (Fig 1). No focal lesions could be seen in the retina in either eye. Visual fields were markedly constricted bilaterally (Fig 2). The ERG was extinguished under photopic and scotopic conditions in both eyes (Fig 3).

The patient was admitted to hospital and underwent a diagnostic vitreous aspiration, which revealed only a sparse infiltrate of lymphocytes, histiocytes, neutrophils, and a few pigmented cells. Cultures for bacteria, fungi, and viruses were negative. Silver strains for fungi and *Pneumocystis carinii* were also negative. While in hospital the patient developed *Pneumocystis carinii* pneumonia with pleural effusion. The diagnosis of AIDS was confirmed by positive serology for HIV by enzyme linked immunosorbent assay (ELISA) and western blot tests and inversion of the T-cell helper/suppressor ratio.

*Figure 2: Goldmann visual fields of patient 1, showing marked, irregular constriction in both eyes.*

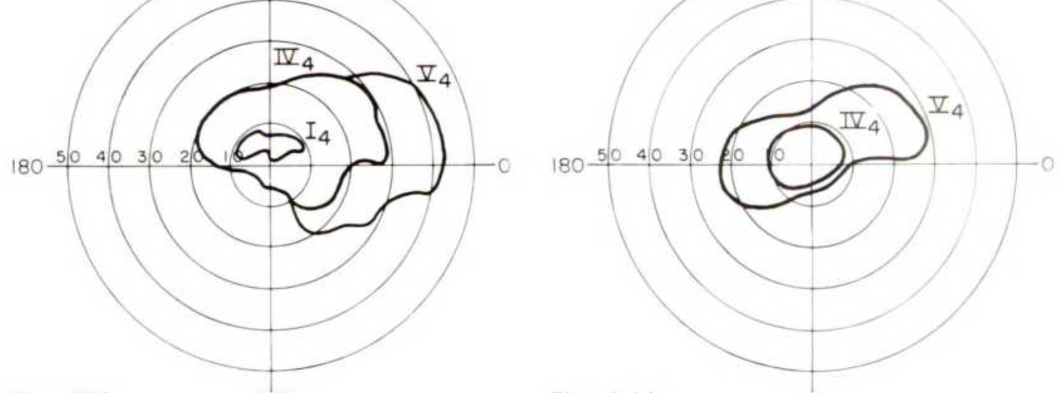

*Figure 2 left*

*Figure 2 right*

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*Figure 3: ERG recordings from left eye of patient 1. Upper tracings show response to single flash; lower tracings show average of responses to 10 repetitions of the flash stimulus. ERGs are extinguished under photopic conditions (left) and scotopic conditions (right).*

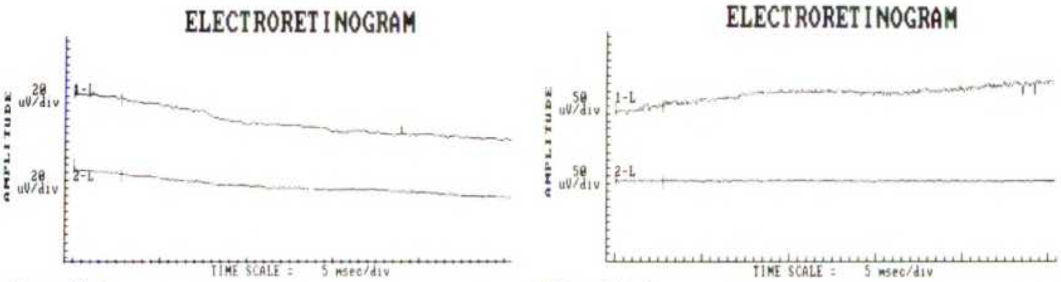


*Figure 3 left*

*Figure 3 right*

*Figure 4: Goldmann visual field, left eye of patient 2. (The patient was unable to respond consistently to the test targets with the right eye.)*

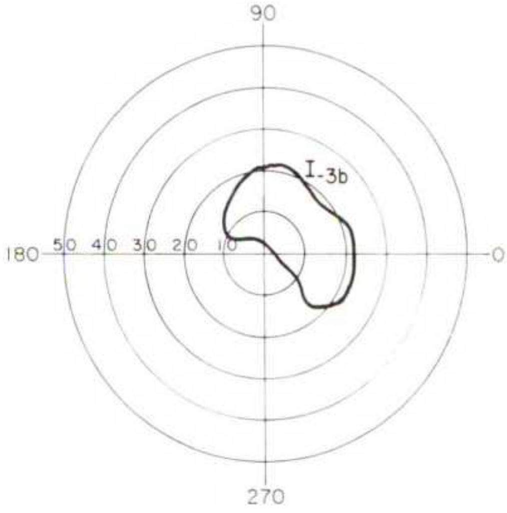
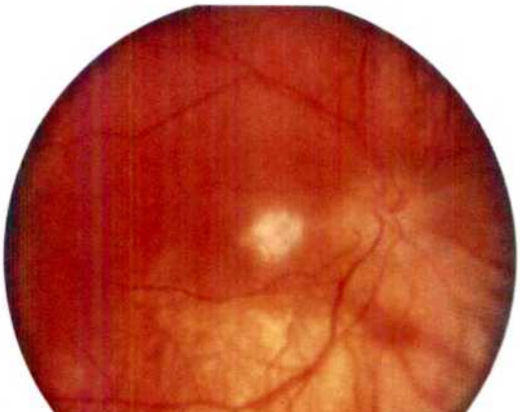


*Figure 5: Fundus photograph of right eye of patient 2. There is a mild vitreous haze and a white intraretinal lesion between the disc and macula.*



The patient was treated with pentamidine and co-trimoxazole. The pneumonia resolved, and his vision showed a small improvement to 20/100 in the right eye and 20/400 in the left eye. On discharge his vision had returned to the level of light perception. Subsequently the patient's general medical condition deteriorated further, and he ultimately died of *Pneumocystis carinii* pneumonia.

### CASE 2

A 35-year-old bisexual male developed *Pneumocystis carinii* pneumonia. A diagnosis of AIDS was confirmed by positive serology (ELISA and western blot tests) and inverted T-cell helper/suppressor ratios. One year later he presented with a six-week history of asymmetrical bilateral loss of visual acuity. On examination his visual acuity was 20/200 in the right eye and 20/30 in the left eye. Visual fields were severely constricted (Fig 4). The anterior segments were normal, but a diffuse vitreous infiltrate was present in both eyes. One white intraretinal lesion, about one-half disc diameter in size, was noted between the macula and the optic disc in the right eye (Fig 5). On fluorescein angiography this lesion blocked fluorescence early but stained homogeneously late in the study (Fig 6). A sector of depigmentation of the retinal pigment epithelium was seen inferonasally in the right eye (Fig 7). No other retinal lesions were seen in either eye.

ERG recordings were significantly reduced in amplitude bilaterally, particularly under scotopic conditions (Fig 8). The maximal B-wave amplitudes elicited from the dark-adapted eyes by an unattenuated white flash stimulus measured 60% and 80% of the lower limit of normal in the right and left eyes, respectively.

*Figure 6: Fluorescein angiogram of right eye of patient 2. During the arterial phase the intraretinal lesion seen in Fig 5 blocks the background choroidal flush (left: 45° photograph). During the late phase of the study the lesion shows persistent fluorescein staining (right: 30° photograph).*

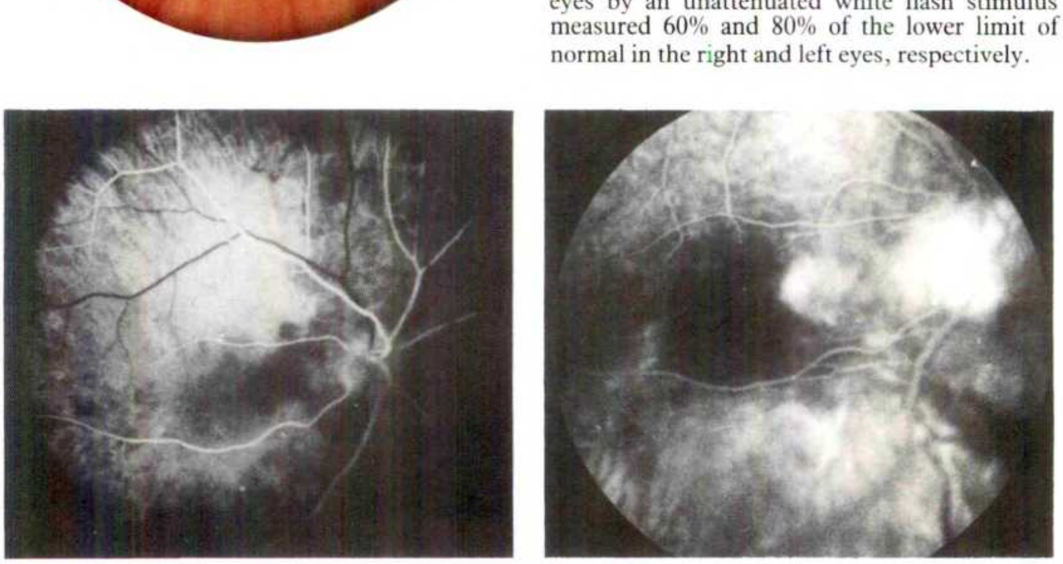


*Figure 6 left*

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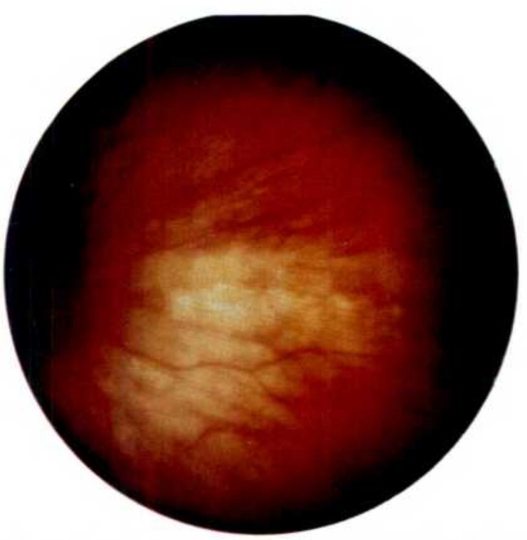

*Figure 7: Localised retinal depigmentation, nasal to optic disc in right eye of patient 2.*

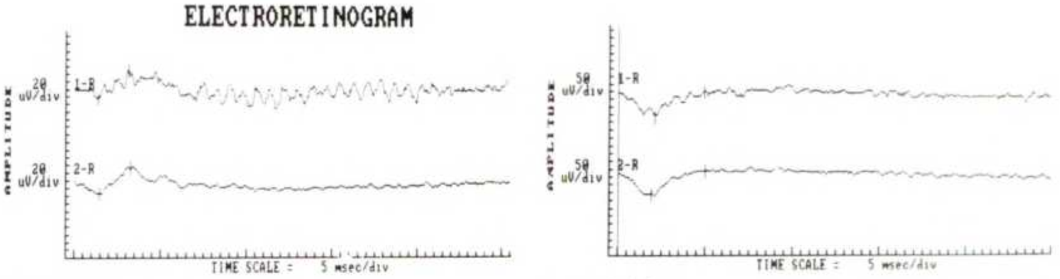

*Figure 8: ERG recordings from the right eye of patient 2. Upper tracings, single flash responses; lower tracings, average of 10 responses. Photopic ERGs show blunted waveforms, with B-wave amplitude at lower limit of normal range (left). Scotopic responses are reduced to 60% of normal (right).*

*Figure 8 left*

*Figure 8 right*

Tests for opportunistic infections (toxoplasmosis, cytomegalovirus, fungi) were negative. A course of ganciclovir produced no effect on visual acuity or on the appearance of the intraretinal lesion. The area of depigmentation of the retinal pigment epithelium appeared to enlarge slightly. The patient remained clinically stable, with reduced vision in the right eye, for several months, but ultimately succumbed to disseminated cytomegalovirus infection.

CASE 3

A 35-year-old black male, employed as a postal worker, was referred for evaluation of rapid visual loss in both eyes over an eight-week period. He was married to a former intravenous drug abuser who had contracted AIDS. Their 9-month old son was born with AIDS. Serological tests, including ELISA and western blot, were positive for HIV infection. The recent medical history was notable for progressive weight loss, anorexia, fatigue, and scattered lymph node enlargement.

An ophthalmological examination showed best corrected visual acuity of finger counting at 1 m in the right eye, and 20/400 in the left eye. The anterior segments were notable for a trace of flare of the aqueous humour and occasional cells in the anterior chambers bilaterally. There was a diffuse vitritis, with a uniform distribution of cells throughout the vitreous cavity, without clumps or skeins. The optic nerves appeared pale. The retinal arterioles appeared narrowed in calibre, but there were no focal retinal or choroidal lesions.

Fundus photographs through the vitreous haze were unsatisfactory. Visual fields, obtained on the Goldmann perimeter, were markedly constricted bilaterally. The ERG was substantially reduced under photopic and scotopic conditions in each eye.

The patient refused admission to hospital. Laboratory studies revealed lymphopenia and immune suppression. A thorough examination for occult bacterial, viral, or fungal infection gave negative results. The patient has remained medically stable, but his vision has continued to deteriorate.

## Discussion

The mechanism of the visual loss in these patients is not known. All three patients showed evidence of vitritis clinically, but there was no sign of ophthalmoscopically visible retinal or choroidal inflammation in two patients and only a very small retinal lesion in the third. Nonetheless the constricted visual fields and reduced or extinguished electroretinograms strongly suggest the presence of widespread retinal dysfunction. In particular, this type of retinal dysfunction may precede the development of the cotton-wool spots, retinal haemorrhages, exudates, and retinal oedema generally understood to comprise the microvascular retinopathy of AIDS. It is conceivable that this dysfunction may represent the ophthalmic equivalent of HIV encephalitis,[2] particularly in view of the electron microscopic demonstration of particles resembling the HIV virion in retinal tissue obtained at necropsy from patients with AIDS,[1] and the isolation of HIV-1[3] and the demonstration of HIV-1 p24 antigen in the aqueous humour of AIDS patients. Recently, Farrell and coworkers reported successful treatment of an HIV-1 positive patient who had an iridocyclitis and retinitis refractory to conventional treatment, with oral zidovudine.[4] They observed resolution of the ocular inflammatory disease, lending further support to our thesis that direct intraocular infection with HIV-1 may be the source of ocular pathology.

Presented in part at the 1987 annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida.

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*British Journal of Ophthalmology*, 1990, 74: 52

# Adult gonococcal keratoconjunctivitis with AIDS

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## Abstract

**Gonococcal eye infection in adults is an uncommon cause of blindness, where prompt diagnosis and effective treatment are essential in the prevention of ophthalmic morbidity. We present a case report detailing the management and complications encountered in this condition in a patient coinfected with human immunodeficiency virus (HIV).**

Adult gonococcal ophthalmic infection is an uncommon but preventable cause of blindness. From 1970 to 1987 three cases, all men, were identified out of 16 600 cases of adult male gonorrhoea seen at the Genitourinary Department of the London Hospital (Whitechapel Clinic). We describe one of these cases to highlight the importance of prompt diagnosis and treatment, screening for concomitant sexually transmitted diseases (STD), and the possible role of human immunodeficiency virus (HIV) infection in modifying host response to gonococcal eye disease.

## Case report

A 42-year-old homosexual telephonist had noticed over a period of 10 days failing vision and greenish discharge from his left eye. He was prescribed antibiotic eye drops at his local casualty department. He failed to respond after a week of treatment, and the other eye became involved. He had no genitourinary symptoms and there was no history of STD. He had, however, lost 8 kg in weight in the previous six months. There was profuse bilateral purulent conjunctivitis, with chemosis and lysis of 90% of the left cornea to a depth of Descemet's membrane, with a flat anterior chamber. Proctoscopy revealed heavy mucopurulent rectal discharge. Gram-negative intracellular diplococci were identified from conjunctival and rectal smears, and confirmed as penicillin-sensitive *Neisseria gonorrhoeae* on culture. Other investigations: specific tests for syphilis were positive, haemoglobin concentration was 108 g/l, white cell count $5{\cdot}3\times10^{9}$/l, normal complement levels and a markedly depressed CD4+ lymphocyte count ($0{\cdot}014\times10^{9}$/l, <1% total lymphocytes).

He was given intravenous cefotaxime 2 g, then 1 g eight-hourly, together with probenecid orally 500 mg six-hourly for 10 days and, initially hourly, cefuroxime 5% eye drops. HIV antibody testing was performed after counselling in view of the severity of the oculogenital infection, significant weight loss, and to help decide on the feasibility of embarking upon protracted reconstructive corneal surgery.

He was found to be HIV-antibody positive, and a temporary tarsorrhaphy of his left eye was performed. Vision in his right eye returned to normal. Although the integrity of the left globe was retained with slow regrowth from the periphery of new but scarred corneal tissue, vision in this eye was limited to counting fingers. He died three months later from the acquired immune deficiency syndrome (AIDS), weighing 33·5 kg, having developed severe intractable diarrhoea and *Pneumocystis carinii* pneumonia.

## Discussion

Gonococcal ophthalmic infection should be considered in the differential diagnosis of purulent conjunctivitis, since anogenital symptoms may be absent, or, if they are present, patients may not readily connect their ocular complaint with genital infection. In the preantibiotic era these cases frequently progressed to corneal perforation within 24 hours.[1] The increasing prevalence of chromosomal-mediated and penicillinase-producing *N. gonorrhoeae* further emphasise the importance of treating this sight threatening infection promptly with effective antibiotics.[2]

Systemic therapy is essential to cover the ocular and genital infections, which almost inevitably coexist, though additional local ocular therapy may help hasten recovery. HIV infection may have contributed to the subtotal corneal perforation, since bacterial infections occur more frequently and severely in the context of immune deficiency.[3] Serious corneal involvement caused by penicillinase-producing *N. gonorrhoeae* has also been reported from the Central African state of Rwanda.[4] However, Rwanda is an area of high HIV seroprevalence,[5] and it is possible that the severity of gonococcal ophthalmic infection encountered was also associated with HIV coinfection.

The complications of ocular gonococcal infection are preventable. A presumptive diagnosis can readily be made on Gram-stained smear, and treatment should be with systemic antibiotics effective against both penicillin-sensitive and penicillinase-producing strains of *N. gonorrhoeae*. Screening for concomitant STD in these patients and their sexual partners should form an integral part of management.

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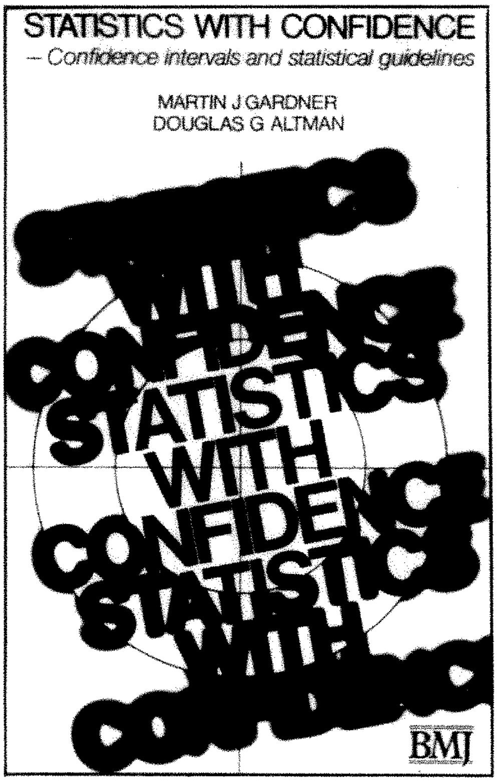
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# Acute tubulointerstitial nephritis and uveitis syndrome in the elderly

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## Abstract

**A case of acute tubulointerstitial nephritis and uveitis syndrome (TINU syndrome) in an elderly woman is reported. The present case demonstrates that this entity originally observed in children, and more recently in adults, may also occur in the elderly. The aetiology and treatment are briefly discussed.**

In December 1985 a 66-year-old Caucasian woman complained of symptoms of anorexia and fatigue. A clinical examination gave normal results. Her blood urea was 8 mmol/l and serum creatinine 133 µmol/l. A proteinuria of 0·9 g/l and some leucocytes in the urine were found. An *x*-ray of the chest, barium meal *x*-ray bone scintigraphy, and abdominal echography were normal.

*Renal symptoms.* One month later admission was necessary because of acute renal failure. Her blood pressure was 190/100 mmHg and temperature 37·4°C. A clinical examination did not reveal other abnormalities. The evolution of the positive blood tests is shown in Table 1. Serological markers for cytomegalovirus, hantavirus, hepatitis B virus antigen, syphilis, streptococci, rubella, salmonella, toxoplasmosis, Epstein-Barr virus, and herpes simplex virus, as well as repeated blood cultures, tests for rheumatoid arthritis factor, immune complexes, and Coombs's reaction were negative. The patient had not been exposed to toxic agents and denied the use of analgesics, antibiotics, or other drugs.

A renal biopsy was carried out. The proximal and distal tubules showed focal areas of destruction, and the interstital tissue was swollen by oedema and a dense infiltrate of lymphocytes, plasmocytes, neutrophils, and some eosinophils; small blood vessels had a swollen endothelium. Immunofluorescence showed the presence of complement in the endothelial layer of the small vessels and protein casts in the tubules (Figs 1 and 2).

Idiopathic acute tubulointerstitial nephritis (AIN) was diagnosed and oral treatment of methylpredisone (32 mg/day) was started. Corticosteroid treatment was gradually decreased and stopped in April 1986. The results of follow-up blood and urine examinations progressively returned to normal (Table I and Fig 3).

*Ocular symptoms.* In June, 5 months after the beginning of the acute renal failure, the patient complained of itching, redness, and pain in the left eye. She was treated with local antibiotic eye drops of Chloransulfa (chloramphenicol 5 mg, sodium sulphacetamide 100 mg/ml, collyrium 10 ml). Two weeks later she complained of loss of vision in the left eye. The visual acuity was 6/6 in the right eye and 6/12 in the left eye. The anterior segment showed keratic precipitates, Tyndall positivity, and posterior synechiae in the left eye. The inferior fornix was hyperaemic, with secretions and follicles. The intraocular pressure was normal. The diagnosis of anterior uveitis was made. Topical treatment of combined neomycin sulphate, polymyxin B, and dexamethasone drops (Maxitrol) together with atropine 1% was started. Two days later persistent posterior synechiae were successfully treated with a paralimbal injection of 0·1 ml of adrenaline (0·1%). Ten days later the visual acuity of the left eye had increased to 6/9. The treatment with Maxitrol eye drops was discontinued because of increasing intraocular pressure. Twenty months later the patient developed a moderate anterior uveitis in the right eye, with a slight Tyndall positive reaction. This inflammatory reaction resolved completely after a few days of treatment with steroid eye drops (Maxitrol). Classical tests for uveitis remained negative.

## Discussion

Since 1975 several cases of an association of acute interstitial nephritis (AIN) with uveitis without any obvious aetiology have been described in children.[1-12] Later a few cases of this oculorenal syndrome have been reported in adult females.[10-14] (Table II). Eighteen out of 28 patients were younger than 20 and the oldest was 56. Our case illustrates that this syndrome can appear at any age. It is interesting to note that the uveitis may appear before, simultaneously with, or after the renal failure. The uveitis appeared as a first symptom in only three cases and simultaneously with the nephritis in five cases. The uveitis was preceded by AIN in 18 cases, with an interval of two to seven months. In 17 cases (70%) the two eyes were involved within two months. In the present case the contralateral eye was involved after 20 months.

In general the anterior uveitis responds well to topical corticosteroid treatment, as the present case confirms. Good results in the treatment of

TABLE I *Evolution of blood and urine analysis data during and after AIN*

| | *Jan 1986* | *Feb 1986* | *May 1986* |
|---|---|---|---|
| ESR (mm/1 h) | 70 | 36 | 13 |
| Haemoglobin (g/dl) | 12·6 | 9·4 | 12·7 |
| Leucocytosis ($\times 19^9$/l) | 9·3 | 9·6 | 4·0 |
| Neutrophils (%) | 57 | 65 | 48 |
| Eosinophils (%) | 3 | 6 | 6 |
| Lymphocytes (%) | 39 | 20 | 29 |
| Blood urea (mmol/l) | 18 | 12 | 10 |
| Blood creatinine (µmol/l) | 592 | 194 | 141 |
| Creatinine clearance (ml/min/1·73 $m^2$) | 8·2 | | |
| Proteinuria (g/l) | 0·5 | 0·5 | 1·0 |
| Glucosuria (g/l) | 3·2 | 2·5 | 1·2 |

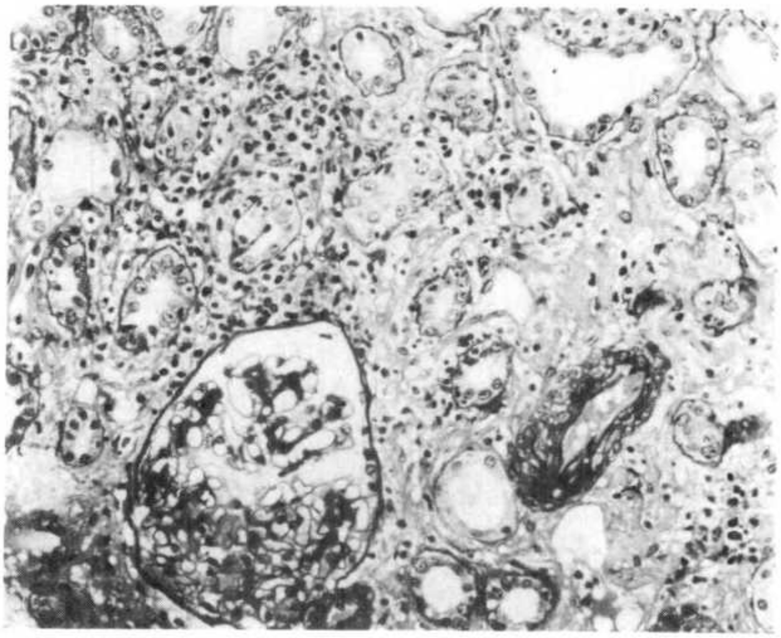

*Figure 1: Photomicrograph of renal biopsy showing normal glomerulus, normal blood vessel, and interstitial infiltrate consisting of inflammatory cells. (PAS, ×200.)*

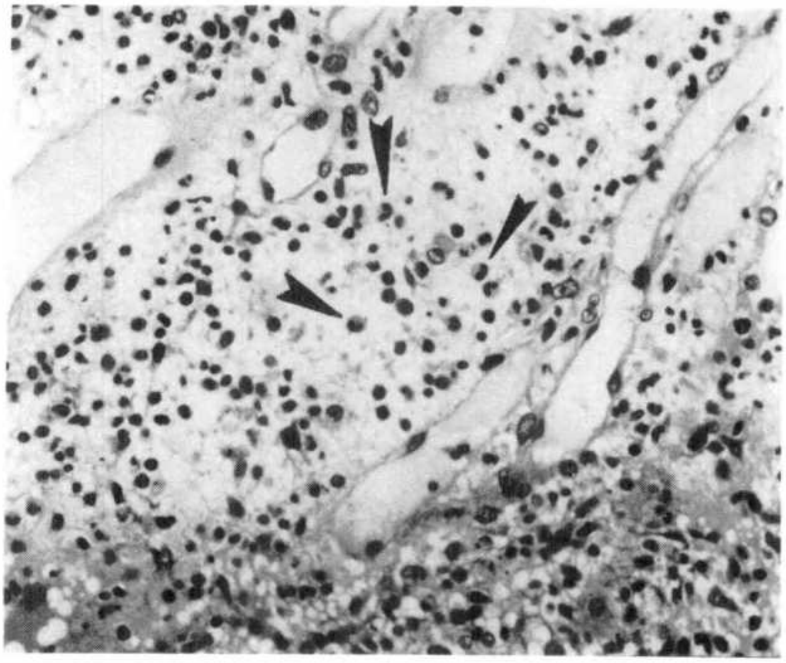

*Figure 2: Photomicrography of the renal biopsy showing the inflammatory infiltrate composed of lymphocytes, plasmocytes, neutrophils, and some eosinophils (indicated by arrows). (PAS, ×320.)*

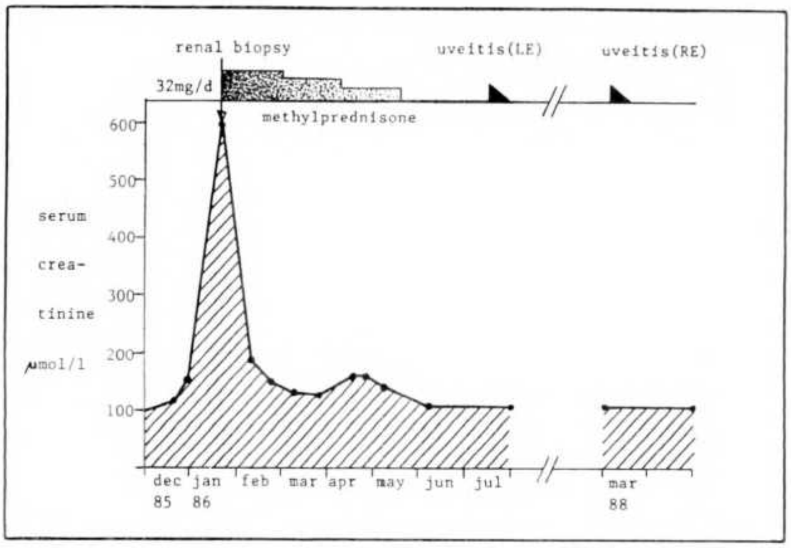

*Figure 3: Clinical course of AIN and uveitis.*

TABLE II *Uveitis in TINU syndrome*

| *Author* | *Year* | *Sex* | *Age* | *Uveitis* *Ant.* | *Post.* | *Unit/bi** | *Months†* |
|---|---|---|---|---|---|---|---|
| Dobrin *et al*[1] | 1975 | F | 14 | + | − | bi | +3 |
| | | F | 17 | − | − | bi | 0 |
| Guesry and Loirat[2] | 1976 | M | 11 | | | | <1 |
| | | F | 10 | | | | +2 |
| | | F | 14 | | | | <1 |
| Kikkawa *et al*[3] | 1977 | F | 13 | + | − | bi | +1 |
| | | F | 14 | + | − | bi | <1 |
| Van Acker *et al*[4] | 1980 | F | 14 | + | − | bi | +2 |
| | | | id | − | + | | +3 |
| Levy[5] | 1983 | F | 10 | | | | |
| | | M | 13 | | | | |
| Roth and Laberke[6] | 1983 | M | 15 | + | +‡ | uni | 0 |
| Burghard *et al*[7] | 1984 | F | 14 | + | − | bi | 0 |
| | | F | 11 | + | − | bi | +3 |
| Steinman and Silva | 1984[13] | F | 27 | + | − | uni | 0 |
| Vanhaesebrouck *et al*[8] | 1985 | F | 15 | + | − | bi | +2 |
| Leumann *et al*[9] | 1985 | M | 14 | + | − | bi | +3 (RE)/+5 (LE) |
| Noël *et al*[10] | 1986 | F | 15 | + | − | uni | +4 |
| | | F | 26 | + | − | uni | −3 |
| | | F | 30 | + | − | uni | +3 |
| Burnier *et al*[14] | 1986 | F | 56 | + | − | bi | −1 (LE)/0 (RE) |
| Mouillon *et al*[11] | 1986 | F | 48 | + | − | bi | −1 (RE+LE) |
| | | | id | | | | +6 |
| | | F | 12 | + | + | bi | 0 |
| Rossenbaum[12] | 1988 | F | 43 | + | +‡ | bi | +7 |
| | | M | 13 | + | − | bi | +3 |
| | | F | 42 | + | +§ | bi | +3 |
| | | M | 54 | + | − | bi | +5 |
| | | F | 52 | + | − | bi | <1 |
| Present case | 1988 | F | 66 | + | − | uni | +5 LE/+20 (RE) |

*Bi=bilateral uveitis diagnosed at the same moment or with an interval of no more than two months between both eyes.
†Months before (−), less than (<), concurrent with (0), or after (+) AIN.
‡Cystoid maculopathy.
§Pars planitis.

interstitial nephritis by oral corticosteroids have been reported.[1 6 7 9-13] Two patients[15] needed cytotoxic agents in addition to steroids for the control of the nephrotic syndrome. In some patients renal abnormalities improved spontaneously.[4 12 14 15] The correlation between the improvement of renal function and corticosteroid administration suggests a beneficial effect of corticosteroids. However, there is no proof of their necessity. In no case has a relapse of the renal disease been observed, whereas the uveitis relapses frequently and after varying periods of time.

The aetiology of the TINU syndrome remains unknown. Classical causes of interstitial nephritis and/or uveitis (as may be shown by serological markers or by bacterial or viral cultures, toxic agents, etc) have not been shown to be responsible for this syndrome. Systemic disease and a drug induced nephritis have been excluded.

An immunological disorder accompanying or causing this syndrome is most likely since: (1) the interstitial infiltrate consists of lymphocytes; (2) a hypergammaglobulinaemia (IgG) is found in most cases; (3) the response to steroid treatment is favourable.

## CONCLUSION

The oculorenal syndrome or TINU syndrome is probably of immunological origin; is accompanied by uni- or bilateral anterior uveitis, which may follow, concur with, or even precede the renal failure; and is most frequently seen in children and adult females, but can occur at any age as the present case illustrates.

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# Morning glory syndrome: a histopathological study

Willem A Manschot

## Abstract

**The clinical and histopathological findings in a case of morning glory syndrome are described. Axial optic nerve retrodisplacement into a peripapillary scleral ectasia (staphyloma), absence of fibrous lamina cribrosa, and optic nerve atrophy were associated with various other, non-inherent ocular developmental anomalies. The uninterrupted lining of the inner wall of the staphyloma by one-layered, normal retinal pigment epithelium proves that the syndrome is not due to a neuroectodermal closure defect.**

The term 'morning glory syndrome' (MGS) was introduced by Kindler,[1] because the papillary region in the affected eye is reminiscent of a (withering) flower of 'morning glory'. Clinical reports[1-14] and four histopathological studies[3 4 8 13] gave rise to a definition of MGS as an 'unilateral malformation involving the optic disc . . . associated with a peripapillary scleral defect, absence of a lamina cribrosa and a recess formed by an axial retrodisplacement of the optic nerve'.[13] These authors postulated that MGS should be considered as a mesodermal disorder. The central posterior scleral malformation may be associated with other intraocular anomalies, of which non-rhegmatogenous retinal detachment is the most frequent.

The rarity of histopathological reports and the rarity of anterior segment pathology, which was not described in previous microscopically studied cases, warrant a report on the clinicopathological data from a further case, which substantiate the postulate[13] that MGS is a mesodermal congenital lesion and not a coloboma of the optic nerve or disc.

## Case report

A male infant aged 7 weeks showed unilateral microphthalmos, central corneal opacity, loss of the anterior chamber, and a mature cataract. Ultrasonography did not reveal an intraocular tumour. The ocular tension was 13 mmHg. Six weeks later, it was 30 mmHg, and 11 weeks later it was 36 mmHg. A CT scan then revealed a retrobulbar cyst connected with the sclera. Enucleation was performed, because retinoblastoma could not be excluded.

### PATHOLOGY

*Macroscopic examination.* The globe measured 19×18×17 mm, the cornea 11 mm. A limbal circular constriction had caused an almost spherical cornea, with a prominence of 4 mm. The optic nerve was noticeably thickened: its diameter was 6 mm, its length 5·5 mm. When its posterior limit was cut for processing through paraffin for identification of possible spread of a tumour, clear fluid escaped from a hole in the new plane of section.

*Microscopic examination.* The cross section of the optic nerve limit showed no evidence of tumour cells. Its central part contained agglomerations of fragments of axons with varicose swellings, and there was reactive proliferation of collagenous connective tissue.

Nitrocellulose embedded serial sections of the globe revealed an abnormal number of keratocytes with deep stromal oedema and absence of Descemet's membrane, and endothelium in the central cornea (Peters' anomaly of cornea). There was total loss of the anterior chamber; the chamber angle, trabecular lamellae and Schlemm's canal could not be observed (Figs 1 and 2A). The dislocated lens showed a hypermature cataract and a partly calcified, anterior and equatorial subcapsular cataract. A rupture in the posterior capsule was filled by connective tissue, originating from a fibrovascular retrolental membrane, which was characteristic of hyperplastic persistent primary vitreous. The membrane contained lens tissue (Fig 2B) and was attached to elongated ciliary processes. Its contraction had caused the circular limbal constriction.

A tent-like totally detached retina contained a falciform fold, which ran from the posterior stalk of the retina to the central part of the retrolental membrane. The fold showed numerous pseudorosettes and defects in the nuclear layers. The macular area contained a reduced but noteworthy number of ganglion cells. The nerve fibre layer was markedly reduced.

The posterior pole was characterised by a

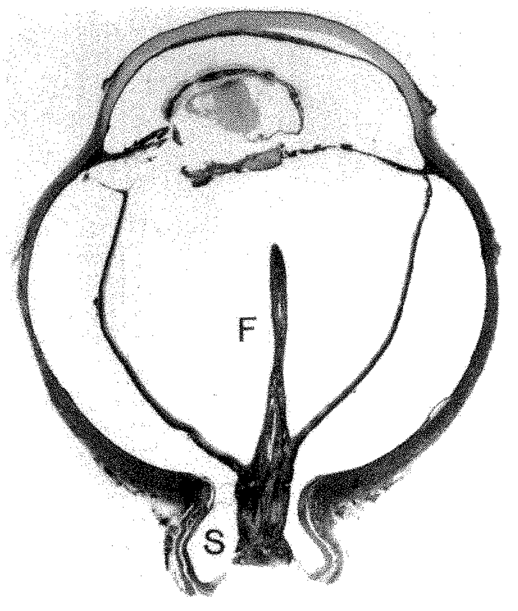

*Figure 1: Horizontal section showing scleral peripapillary staphyloma (S) with retrodisplaced optic nerve, total retinal detachment with axial stalk, and posterior part of falciform fold (F). (Nitrocellulose section, H and E, ×4.)*

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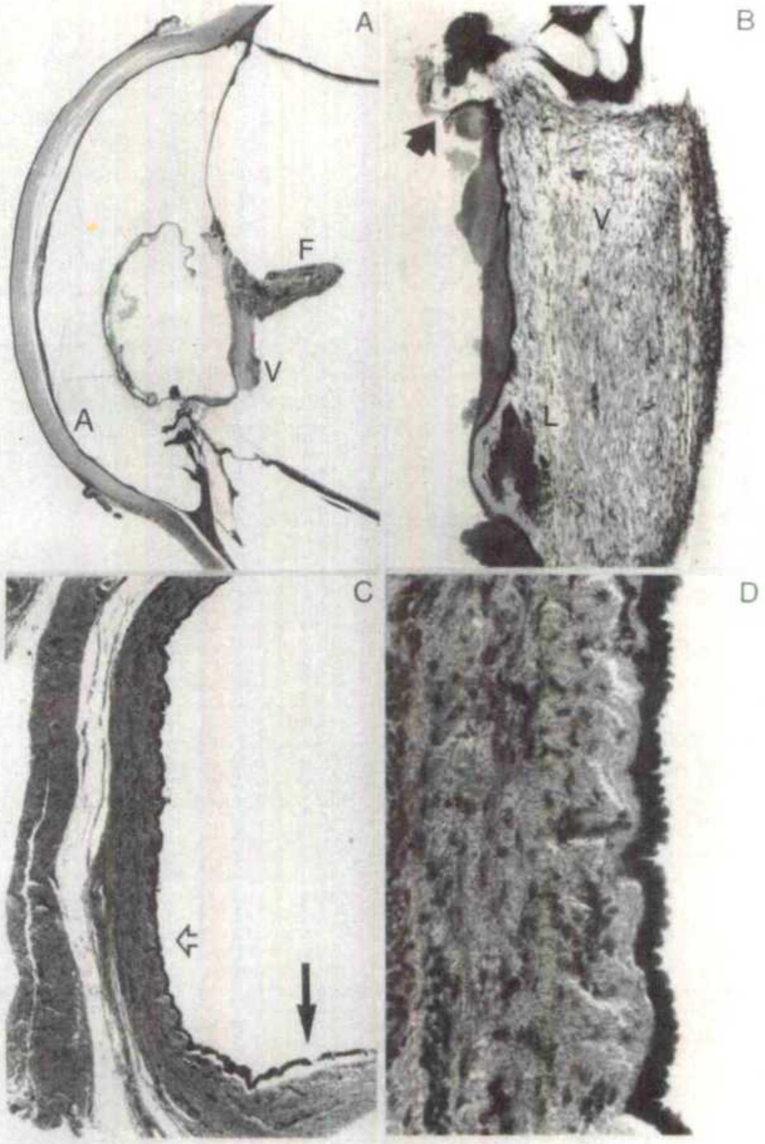

*Figure 2: A: Total anterior synechia (A), ectopic cataractous lens, hyperplastic persistent primary vitreous (V), elongated ciliary processes, anterior part of falciform fold (F). (H and E, ×6.) B: Posterior lens capsule with rupture (arrow), lens substance (L) in hyperplastic persistent primary vitreous (V). (H and E, ×50.) C: Nasal wall of peripapillary staphyloma lined by retinal pigment epithelium. Note inner and outer scleral layer. Black arrow: peripheral part of base of staphyloma. Open arrow: pigment epithelium represented in Figure 2D. (H and E, ×40.) D: Detail of Figure 2C indicated by open arrow (×260).*

4 mm deep peripapillary, funnel shaped scleral ectasia (staphyloma); its diameter was 5 mm. The inner wall of the ectasia and the periphery of its base were uninterruptedly covered by one layer of normal retinal pigment epithelium (Figs 2C, 2D). Remnants of the choroid could not be recognised below the layer of pigment epithelium. The extended inner and outer scleral layer were separated by a narrow fissure. The outer layer merged into the optic nerve dura; the inner layer surrounded the retrodisplaced optic nerve head in the base of the recess. Small numbers of smooth muscle cells could be recognised within the outer scleral layer, while clusters of fat cells could be observed within the narrow fissure. The stalk of the detached, non-rhegmatogenous retina arose from the nerve head and ran completely free from the inner wall of the recess axially through the scleral aperture into the lumen of the eye. The central retinal vessels and their first branches could be recognised within the stalk. The first branching of the central vessels had occurred at its normal site adjacent to the neuroectodermal lamina cribrosa, in which no fibrous tissue was found. Anomalous blood vessels were not observed within the retinal stalk.

*Histopathological diagnoses.* Peters's anomaly of cornea, aplasia of the chamber angle, congenital cataract, hyperplasia of persistent primary vitreous, total detachment of atrophic, dysplastic non-rhegmatogenous retina, falciform retinal fold, axial optic nerve retrodisplacement into peripapillary scleral staphyloma, absence of fibrous lamina cribrosa, and optic nerve atrophy.

## Discussion

The first description of MGS is attributed to Handmann,[2] who reported six cases of identical (?) hereditary anomalies of the optic disc. Heredity[14] and bilaterality of peripapillary staphylomas[14 15] have been described exceptionally. The normal visual acuity in some of these cases justifies some doubt whether they were of MGS.

The main clinical features of MGS are (1) an apparently enlarged, sometimes excavated optic disc with a central mass of whitish-grey tissue; (2) a disc surrounded by a peripapillary scleral staphyloma, which in its turn may be surrounded by an elevated peripapillary ring of white, often pigmented tissue; (3) attenuated, branching arterial and venous retinal vessels, radiating from below the epipapillary mass of whitish tissue. These radiating vessels often appeared to be more numerous than the retinal vessels in the fellow eye and showed fewer bifurcations. Visual acuity is poor. Systemic defects rarely accompany the ophthalmoscopic findings.

The main histopathological features of MGS are axial retrodisplacement of the optic nerve and a peripapillary, funnel shaped scleral staphyloma. The scleral ectasia is thought to be due to a developmental central posterior scleral anomaly. The optic nerve sheaths may be affected and may be partly replaced by fibroadipose and smooth muscle tissue. The fundamental observation in the present case of uninterrupted retinal pigment epithelium covering the entire inner wall of the staphyloma confirms that MGS is not due to a neuroectodermal closure defect. An identical continuous inner layer of pigment epithelium has been described by Cogan.[8] Rack and Wright[9] and Dempster *et al*[13] reported respectively a 'broad collar of collagenous tissue in which pigmented cells are numerous' and 'nodules of metaplastic pigment epithelium which formed a ring around the neck of the recess', but not a continuous layer of pigment epithelium overlying the inner wall of the recess.

A non-rhegmatogenous retinal detachment has been reported in five cases.[1 6 11] The present sixth case with its total detachment and axial stalk within the staphyloma seems to substantiate the postulate that these non-rhegmatogenous detachments in MGS most probably are due to continuous traction exerted by the gradually increasing axial retrodisplacement of the optic nerve. A primary non-attachment of the retina appears unlikely. Rack and Wright[3] and Cogan[8] depicted macroscopic and microscopic features of the radiating folds round and in the entrance of the peripapillary staphyloma.

The frequently described unduly numerous attenuated branches of the central vessels, which radiate peripherally in a sometimes striking straight course from below the central white tissue, are most probably the normally more peripherally situated branches after their second ramification. In MGS they are more centrally located by the retrodisplacement of the optic nerve head, which was 4 mm (!) in the case of Rack and Wright[3] and in the present case.

The disc appears generally enlarged. It should, however, be realised, that in most cases the nerve head cannot be observed owing to its axial retrodisplacement and the whitish tissue which overlies and sometimes surrounds the nerve head.[1-14] This whitish tissue consisted in all histopathologically studied cases, including the present case, of folded retina with glial, fibrous, and pigment epithelial proliferation.

The depressed or elevated peripapillary, whitish often hyperpigmented ring represents the entrance of the peripapillary staphyloma. Either the retina is attached to the wall of the aperture, or retinal folds or a retinal stalk pass freely through the aperture. An elevated peripapillary ring consists of pseudofibrotic metaplastic retinal pigment epithelium, covered by a degenerated retina. It hides the aperture to the ectatic lumen.

A persistent hyaloid artery has been reported twice.[9,11] The present case showed a thick layer of retrolental fibrovascular tissue, originating from hyperplastic persistent anterior primary vitreous. It was connected with stretched ciliary processes, and it had ruptured the posterior lens capsule.

Ipsilateral Peters's anomaly of cornea has so far not been described in MGS. In avian embryos the 'mesectoderm' of the head derived from the neural crest is the source of most ocular tissues. The corneal endothelium and keratocytes are entirely so, the sclera is almost entirely of neural crest origin, while the vitreous has an unquantified derivation from the neural crest.[14] Comparative studies indicate that normal crest development is fundamentally similar in all vertebrate embryos.[15] Experimental evidence necessary to define clearly the origin of ocular tissues in mammals is not yet available, but recently experimental work has provided direct evidence that the neural crest contributes to cranifacial development in mammals.[16] The association of Peters's anomaly of the cornea and hyperplasia of persistent primary vitreous with the posterior scleral malformation in MGS may be purely coincidental, but it might also be a manifestation of a neural-crest-derived 'mesoectodermal' disturbance: a 'neurocristopathy'.[17]

Some contractile peripapillary staphylomas have been reported.[18-20] Their movements can be explained by the presence of heterotopic smooth muscle tissue in the posterior sclera or choroid.[21] This smooth muscle tissue is often accompanied by heterotopic adipose tissue in the choroid and/or in the enlarged distal region of the optic nerve and its sheaths. It occurred unilaterally in 24 of 26 cases.[21] Smooth muscle cells and fat cells were also observed in the ectatic scleral tissue of the peripapillary staphyloma in the present case.

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# Microphthalmos with colobomatous orbital cyst: clinical, histological, immunohistological, and electronmicroscopic findings

W Lieb, R Rochels, U Gronemeyer

**Abstract**

**A case of unilateral microphthalmos with orbital cyst is presented. This rare and severe malformation is a non-hereditary disorder. Pathologically it represents a failure in the closure of the embryonic fissure at the 7–14 mm stage of gestation. Staining for neurofilaments permitted the identification of rudimentary optic nerve fibres within the gliomatous cyst wall. Special stains for glial fibrillary acidic protein as well as scanning and transmission electron microscopy were used to characterise the neuroglial cell lining of the cyst wall, and to show microvilli on its inner surface.**

Numerous case reports can be found on microphthalmos and orbital cyst.[1-12] This nevertheless rare entity is defined as a cystic mass lined by neuroectoderm protruding through a coloboma of a microphthalmic eye. It appears usually during the first few months after birth and is usually unilateral, though bilateral cases have been described.[13] There is no sex prevalence and in contrast to a similar malformation in animals the majority of cases are non-hereditary[14] and not associated with other malformations. Some associated other findings have been described.[15] There is even a report of an astrocytoma of the optic nerve arising in a case of microphthalmos and orbital cyst.

Although it is a clearly defined entity, many of these lesions are still misdiagnosed for an orbital tumour. Clinical examination is in most of the cases the key to making the diagnosis. Nowadays imaging techniques as A and B scan ultrasonography,[16] computed tomography,[17] and magnetic resonance imaging[15] are helpful in supporting the diagnosis and in differentiating it from a congenital cystic eye,[18] meningocele, or meningoencephalocele, primary optic nerve sheath cysts,[13] and teratomas of the orbit. Orbital teratomas quite often have a cystic appearance and are usually benign, though malignant changes have been reported.[19]

In our case we had the opportunity to use immunohistochemical techniques as well as scanning and transmission electron microscopy to study this unusual lesion.

## Case report

A 1-month-old white female child was referred with the diagnosis of a right orbital mass. The child was the product of a normal pregnancy and labour. Her general health as well as her sensory and motor development were normal.

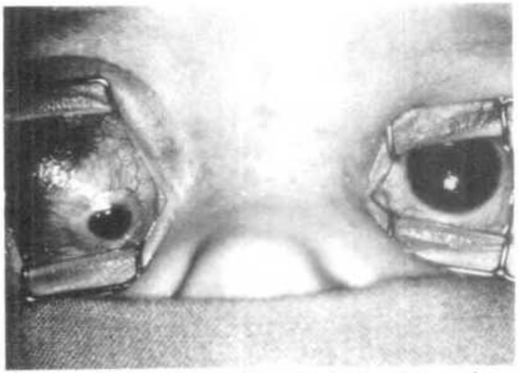

*Figure 1: Dark bluish mass involving the superotemporal part of the right orbit. The microphthalmic globe is displaced inferonasally.*

Since birth the parents had noticed a slowly progressive protrusion of the right globe. A general paediatric examination revealed a normally developed otherwise healthy child.

On ophthalmological examination the child did not fixate with the right eye and there was a superficially vascularised mass occupying the superotemporal part of the orbit, which, except for a small globe rudiment inferonasally, transilluminated. The microphthalmic globe, measuring approximately 8 mm in diameter (Fig 1), had a diffusely clouded cornea. An iris coloboma was suspected, and there was a white vascularised membrane in the pupil. The left eye was entirely normal.

A and B scan ultrasonography (Digital B, Cooper Vision, and 7200 MA Kretztechnik) was performed and showed a small globe filled with medium to highly reflective tissue, and there was a large cystic structure attached to the globe occupying most or the orbit. The clinical diagnosis of a microphthalmos and orbital cyst was made and confirmed by magnetic resonance

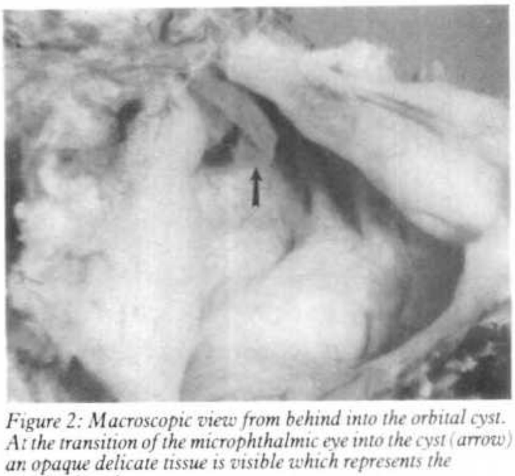

*Figure 2: Macroscopic view from behind into the orbital cyst. At the transition of the microphthalmic eye into the cyst (arrow) an opaque delicate tissue is visible which represents the dysplastic retina.*

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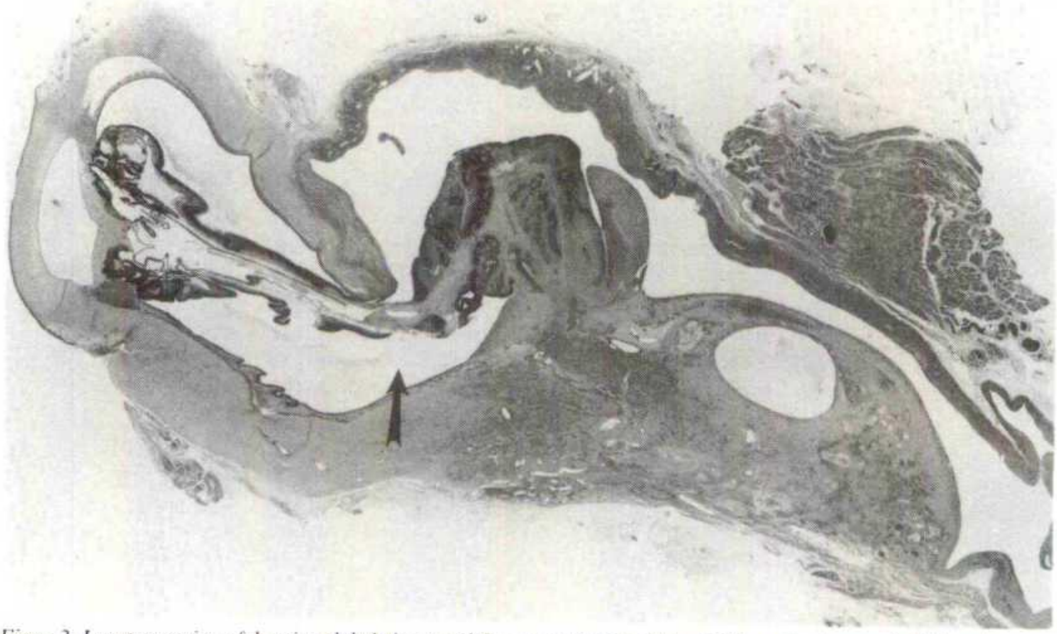

*Figure 3: Low power view of the microphthalmic eye and the communicating orbit cyst. The section in a saggital plane shows clearly the colobomatous defect (arrow) and the dysplastic retina attached to a gliomatous mass in the cyst wall. (H and E, ×20.)*

imaging (MRI) and orbital computed tomography (CT).

On the parents' request the grossly malformed blind eye was enucleated. The enucleation and removal of the orbital cyst was uneventful. However, since the cyst reached up to the orbital apex, it was impossible to remove the furthest posterior part of it.

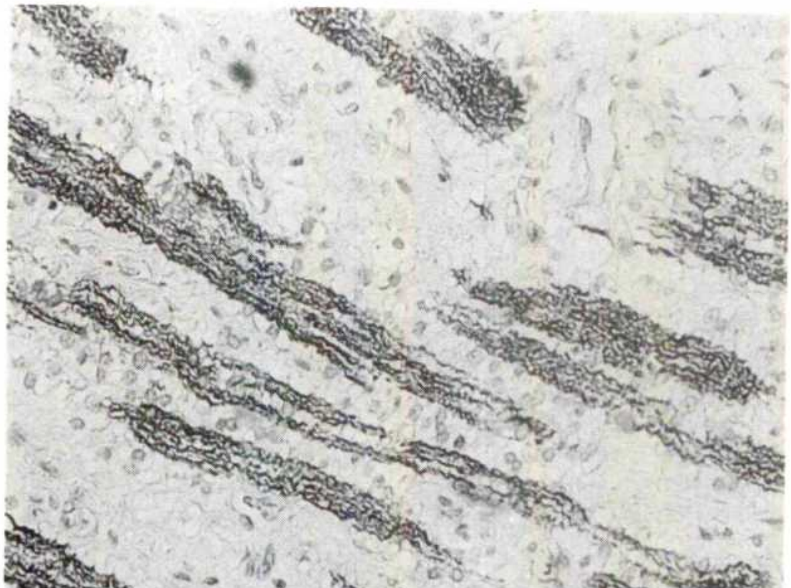

*Figure 4: Stains for neurofilaments demonstrate optic nerve fibrils within the cyst wall in the area where the gliomatous dysplastic retina inserts into the gliomatous mass. (Immunoperoxidase stain, ×50.)*

## PATHOLOGY

Macroscopic examination revealed a 17·5×16 ×18 mm large collapsed cystic mass. In its inferionasal part was a 11×10×9 mm globe. The small globe as well as a solid hard structure in the nasal wall of the cyst did not transilluminate. At the transition from the globe to the cyst an opaque fine tissue was visible (Fig 2). The specimen was cut in a sagittal plane (Fig 3) and processed in serial sections.

Microscopic sections showed a moderately thickened stratified squamous epithelium of the cornea; Bowman's layer was absent; the corneal stroma was still rather cellular; the endothelial cell count was normal, but the endothelial cells had a vacuolar cytoplasm. The endothelium covered the anterior aspect of the chamber angle structures. The trabecular meshwork and Schlemm's canal were not yet differentiated. On the posterior iris surface elongated ciliary processes were seen, which were connected to a dysplastic retina with malformed rosettes. In between the folded retina there were remnants of the lens epithelium and posterior lens capsule, with only few particles of cortex material. Remnants of the anterior and posterior tunica vasculosa of the lens could be seen.

The inner surface of the microphthalmic globe was covered by pigment epithelial cells. The dysplastic retina was folded and reached through a large defect in the posterior wall of the globe into the large orbital cyst (Fig 3). Here the folded

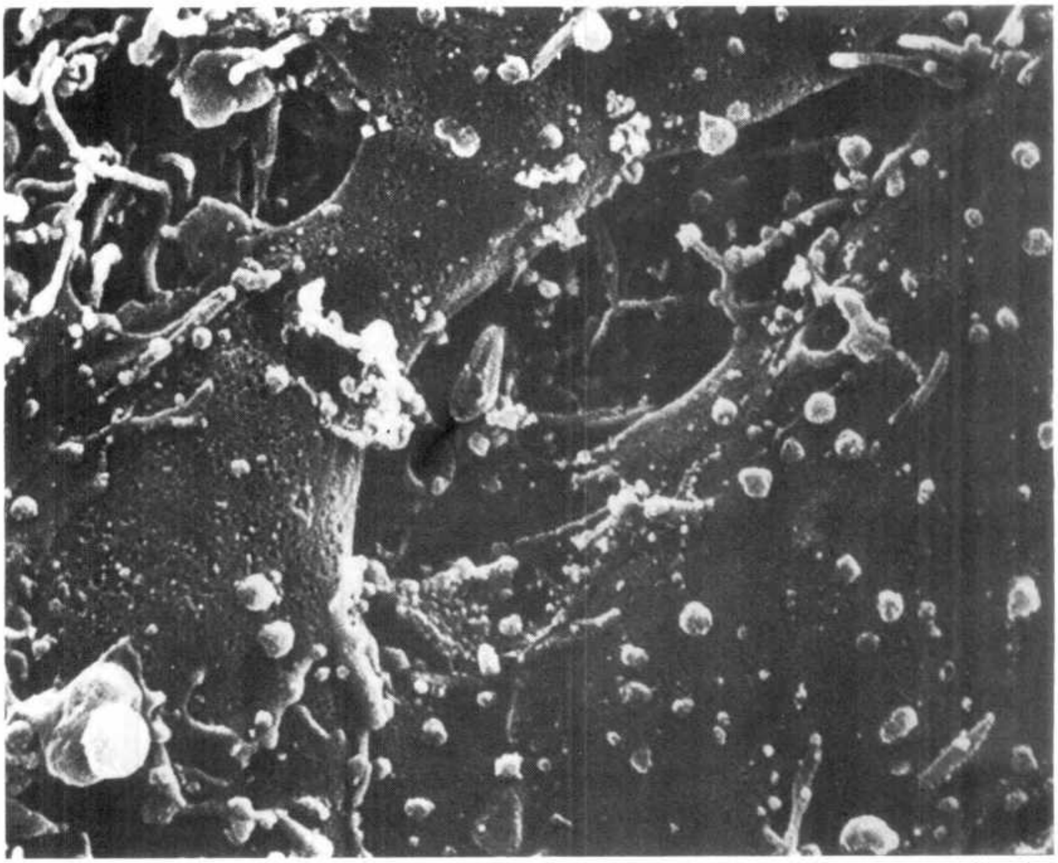

*Figure 5: Scanning electron microscopy of the inner cyst wall. There are numerous layers of flat glial cells with microvilli on the cell surface. (×10 400.)*

retina was connected to a mass of glial tissue extending into the cyst lumen. Choroid, Bruch's membrane, and the retinal pigment epithelium extended through the coloboma but ended abruptely a short distance into the cyst. The thick scleral tissue continued to cover the orbital cyst, whose inner wall was lined by a thick layer of highly vascularised glial tissue. On the posterior aspect of the cyst skeletal muscle fibres and adipose tissue could be identified. To define the inner lining of the cyst better we stained for glial fibrillary acidic protein (GFAP), which stain diffusely the inner cyst wall. In addition the glial elements of the dysplastic retina were stained. GFAP is the major intermediate filament subunit in the mature astrocytes.

Since remnants of optic nerve tissue could not be found on routine histological examination, we stained for neurofilaments. These showed as fine fibrillary structures in the nasal cyst wall deep to the glial mass connecting to the retina (Fig 4). The neurofilament protein consisted of three

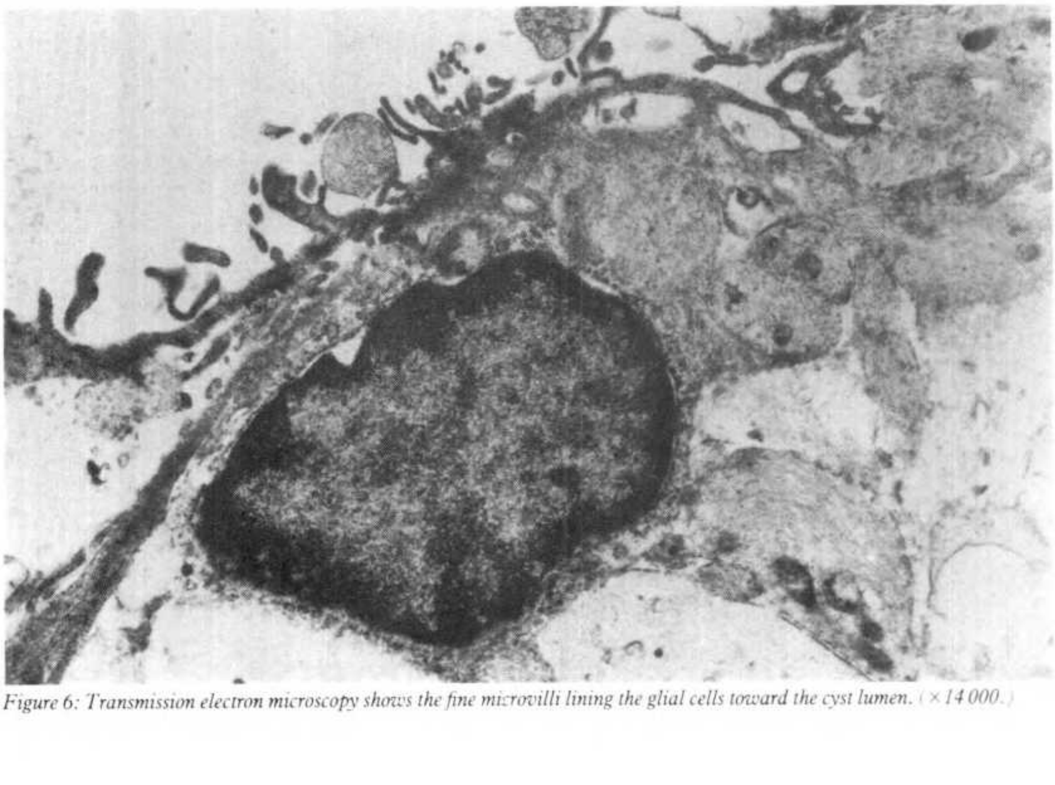

*Figure 6: Transmission electron microscopy shows the fine microvilli lining the glial cells toward the cyst lumen. (×14 000.)*

polypeptides ranging in their molecular weight from 70 to 200 K.

Scanning electron microscopy of the inner cyst wall showed flat cells in several layers with multiple button-like excrescences on their surface (Fig 5). Transmission electron microscopy identified clearly these structures seen on scanning EM as fine microvilli at the surface of the glial cells (Fig 6).

## Discussion

Microphthalmos with colobomatous orbital cyst is a rare differential diagnosis of congenital orbital tumours.[12 13] It is usually detected in the early neonate period. The typical presentation is a protruding mass in the inferior orbit associated with an often quite severely malformed microphthalmic eye. In some instances the eye cannot be identified clinically[20]; the globe may be completely surrounded by the cyst, or there might be a very rudimentary displaced microphthalmic eye. Colobomatous orbital cysts are generally unilateral, though bilateral cases have been described.[13] A number of associated other malformations have been reported. However, as in our case, it may be an isolated malformation.

So far there is no convincing evidence of an underlying chromosomal abnormality. Whereas in earlier times many of these lesions have been diagnosed during surgical removal, nowadays this entity is recognised clinically. The various imaging techniques – A and B scan ultrasonography,[15] computed tomography,[16] and magnetic resonance imaging[14] – enable us to differentiate this entity more easily from other benign or malignant orbital masses in childhood. As early as 1908 Natanson[7] and later von Szily[21] had recognised the pathogenesis of this disorder. Further studies by Badtke and Tost[2 22] in laboratory animals showed the pathoanatomical features of these defects.

A number of authors have given their theories on the pathogenesis. According to Mann[23] the normal optic vesicle tends to invaginate prior to the 6–7th embryonal week. During this period colobomatous cysts develop. The fetal fissures start to close usually at the 11 mm stage and closure is complete by the 18 mm stage. Since the inner layer of the optic cup develops faster, a slight eversion along the margins of the fissure is produced. If there is fully formed retina at the margins of the fissure, this prevents closure of the optic cup. If closure fails, a typical coloboma without overlying retina develops. In cases where no closure takes place, the edges of the retinal layers may further distend, fluid separates the two retinal layers, and a cyst forms. Finally the two separate cystic layers coming from the nasal and temporal side of the coloboma will blend into one large cyst. The fact that the cyst enlarged with time is probably due to excess fluid production by the glial cells. One argument for this is that the glial cells lining the orbital cyst inner surface show pronounced formation of microvilli. The cyst fluid might be produced by the glial tissue. In some cases a communication between the cyst and the subarachnoidal space has been thought to be responsible for continuous cyst enlargement. In most cases, however, no true communication could be demonstrated. Another mechanism for progressive enlargement of the cyst is extensive proliferation of glial tissue, eventually filling and expanding the cyst cavity.[24] In most cases, however, no communication could be demonstrated despite enlargement of the cyst.

Immunohistochemistry using stains for GFAP demonstrates nicely the glial nature of the cyst wall, composed mainly of astrocytes. Stains for neurofilaments make it possible to identify a bundle of optic nerve axons. Modern methods of immunohistochemistry and scanning and transmission microscopy are valuable tools in addition to older histological techniques for studying congenital malformations of the eye and orbit.

We are grateful to Professor Dr B Daicker from the Ophthalmopathologic Laboratory of the University Eye Hospital in Basel for valuable advice and support in performing macroscopic sections and scanning electron microscopy. The scanning EM sections were made in the REM Lab of the University Basel (Professor Dr Guggenheim). We thank Professor Dr M Tost, of the University Eye Hospital, Halle (GDR), for reviewing the slides and giving us his expert opinion on this case.

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# LETTERS TO THE EDITOR

## Amitosis in human donor corneal endothelium – a serendipity?

SIR,—It is generally accepted that the human corneal endothelium does not usually replicate, Kaufman *et al*[1] described a single dividing (amitotic) cell in the donor cornea of a 50-year-old man, and more recently Laing *et al*[2] reported a putative mitotic figure by clinical specular micrographs in a case of graft rejection. They suggested that mitosis represents an additional healing mechanism to repair by cell reorganisation, migration, and enlargement. Since the human endothelium cannot at present be studied continuously but at short intervals in vivo, a given cell cannot be monitored at different phases of division. Hence evidence for mitosis or amitosis must be circumstantial and based on isolated clinical or histological observations. Any report of suspected cell division adds to this circumstantial evidence.

We wish to report the finding of binucleate cells by scanning electron microscopy (SEM) in the endothelium of purportedly normal adult and infant donor corneas. One cornea was from a 65-year-old woman with a normal ocular history. The cause of death was cardiac failure, and the globe was enucleated 12 hours post mortem. The other was from a case of cot death at the age of 3 months. The eye was enucleated four hours post mortem. A corneoscleral button was excised from each and prepared for SEM. During random scanning a single binucleate cell was found in the adult corneal endothelium. It was larger than the adjacent cells and its posterior plasmalemma appeared intact. At higher magnification, an apparent cleavage line was visible between the nuclei (Fig 1). Owing to the suspicion that mitosis occurs in infant corneas used for keratoplasty,[3] dividing cells were specifically sought in the infant endothelium. A single binucleate cell was found (Fig 2).

Recently coalescence of endothelial cells, which creates bi- or multinucleate cells, has been implicated as a repair mechanism.[4] However, as indicated by other observers,[5] the binucleate state is equally explained by nuclear division. A consideration of the binucleate state should include normal mitosis, amitosis, cell fusion, cell rest, or indeed artefact. The lack of cytoplasmic cleavage in the cases reported here suggests incomplete mitosis or amitosis – a process in which the nucleus divides without cytoplasmic cleavage.

It is not known when human corneal endothelial cells lose their ability to divide, and conclusions regarding endothelial cell regeneration cannot be drawn from the chance findings of binucleate cells. However, the circumstantial evidence to date indicates that complete cell division, if it occurs in the mature corneal endothelium in vivo, is very infrequent and cannot adequately replace damaged or dead cells. Therefore all care should be taken to avoid the loss of cells during the preparation of donor corneas for transplantation, and, if methods of handling infant corneas (which possess twice the number of cells of adult corneas and which may be in the process of cell multiplication) can be improved, then the very young donor cornea is to be recommended.

The authors wish to thank Mr R J Buckley, FRCS, for reading the manuscript, the Department of Medical Illustration for photographic processing, and Miss Sheila Work for secretarial assistance.

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## Measurement of corneal diameter

SIR,—The measurement of corneal diameter was the subject of a recent paper by Robinson *et al*.[1] The ocular dimensions, and changes due to normal or abnormal processes, are of particular interest to ophthalmology.[2] While Robinson *et al*[1] address important issues, several aspects of their paper deserve further comment.

The definition of corneal diameter is critically important to the resultant measurements and, arguably, to the biological import of such measurements. Previous values of corneal diameter reflect a lack of uniformity in definition and method.[3] Robinson *et al*[1] apparently adopted the horizontal visible iris diameter (HVID) as their definition of the horizontal corneal diameter (HCD).

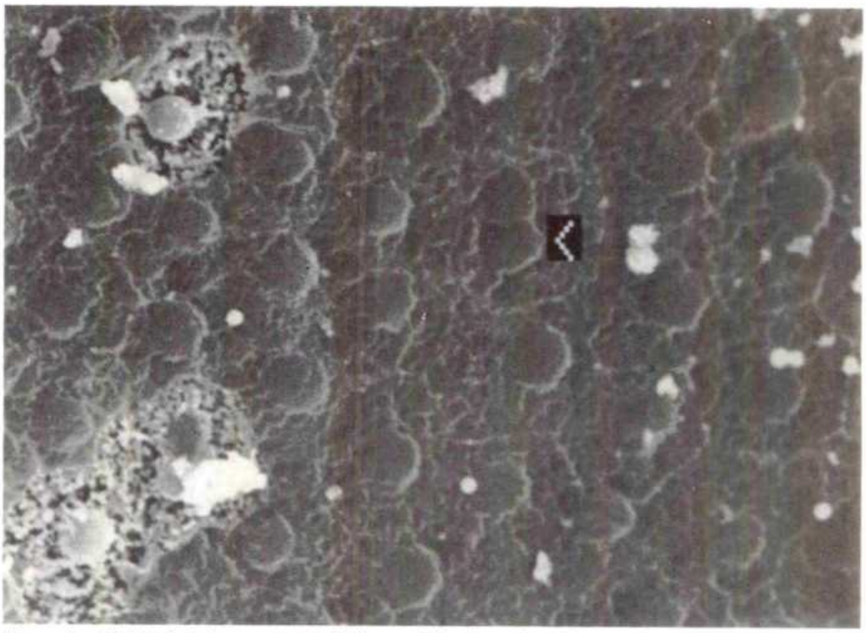

*Figure 1: SEM of adult corneal endothelium (x 860). Arrowhead indicates binucleate cell.*

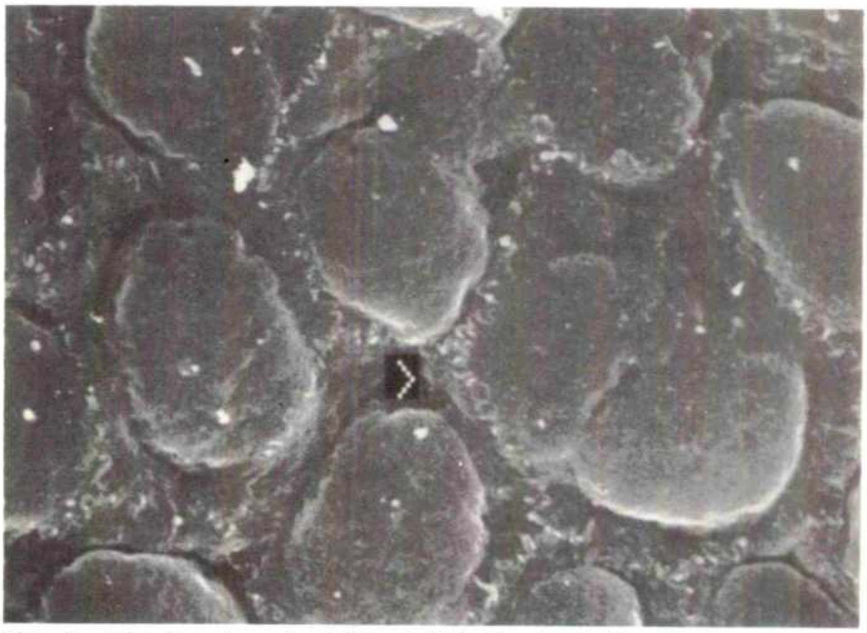

*Figure 2: SEM of infant corneal endothelium (x 2800). Arrowhead indicates binucleate cell with cleavage line.*

Anatomically HCD can be measured with reference to the external scleral sulcus, a small furrow at the corneoscleral transition zone.[3] The visible iris will vary with peripheral thickness and transparency, and thus HVID would be expected to be a variable underestimate of HCD. Parenthetically, plane-projected distances such as HVID and HCD underestimate the true curvilinear surface distance.[4] The difference between HVID (measured by Robinson *et al*[1]) and HCD may have non-trivial effects on recording corneal size. For example, peripheral corneal thickness changes with age,[5] and measurements of HVID may not accurately reflect corneal growth.

The authors claim (p 572) that 'the photographic method is more accurate: diameters may be measured to the nearest 0·05 mm from the photographs compared with ±0·25 mm with calipers or ±0·5 mm with a ruler'. The photographic method has undoubtedly the best *resolution*, and hence probably the best *repeatability*, but nowhere do Robinson *et al*[1] establish the superior *accuracy* of the photographic method. In other words, photographic determination may provide HVID estimates of good precision, but HVID itself may be an inaccurate indicator of HCD, or the true corneal diameter. One study[2] found that HVID<HCD, and, while HVID and HCD are reasonably correlated, HVID can be an inaccurate predictor of HCD. For an HVID= 11·6 mm, the 95% confidence range for HCD was 12·1 to 13·7 mm.

The problem of reconciling the need for measurement accuracy with that of simplicity and suitability for clinical application was nicely resolved by Martin and Holden, of Sydney, Australia.[3] Martin found that fluorescent tubes can be positioned in front of the eye such that the catoptric images are discontinuous at the external scleral sulcus, thus disclosing the true corneal diameter (HCD) as the horizontal distance between the discontinuities.[3] Combined with the advantages of photography, Martin's method offers a simple yet acurate means of monitoring corneal diameter.

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SIR,—We thank Dr Kwok for his interest in our article.[1] We agree that the definition of corneal diameter is critically important, but unfortunately no satisfactory definition is forthcoming. The problem is exemplified by the statement, 'there is a gradual transition of clear cornea to opaque sclera, the superficial third becoming opaque earlier than the deeper two thirds'.[2] Later on these same authors comment on the difficulty of defining this junction histologically, as there is a gradual transition from cornea to sclera. It is implicit therefore that no single measurement can adequately define the corneal boundaries, and it is not surprising that a wide range of values is quoted in the literature.[3] We therefore elected to measure the parameter most readily identified – that is, white-to-white.

The long-term aim of our study, albeit not stated in the article, was to develop a technique using a portable apparatus, which would enable 'corneal diameter' to be measured simply and repeatedly in preterm neonates and children, some of whom may have ocular malformations or infantile glaucoma. We did not use the corneoscleral furrow as a measuring point for the following reasons: it is difficult to see; there is no information as to its presence in the neonate, infantile glaucoma, or other globe malformations; and finally its relationship to limbal histology has not been defined. We do not doubt the value of the method using catoptric imagery and the corneoscleral furrow but question its application to the study of corneal growth in preterm neonates. Martin and Holden[4] used catoptric imagery to measure both the white-to-white and corneal diameter in 50 eyes, but eye casts were made in only five of these patients. For these eyes no comparison was made between either the white-to-white or corneal diameters measured using catoptric imagery and the white-to-white or corneal diameter in vivo.

We concur with Dr Kwok that we have not established the superior accuracy of our method as a measure of the 'true' corneal diameter, but for the reasons stated above this probably cannot be contained in a single measurement.

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# BOOK REVIEWS

**Vitamin A Supplements.** Prepared by a WHO/UNICEF/IVACG Task Force. Pp. 24. Sw fr 8.00. World Health Organisation: Geneva, 1988.

This short publication gives precise information on the rationale and recommendations for the treatment and prevention of vitamin A deficiency. Details of alternative strategies for the prevention of xerophthalmia are discussed as well as matters pertaining to the logistics of implementing various programmes. It is essential reading for all physicians involved in child care in developing countries.

A FOSTER

**A Colour Atlas of AIDS and HIV Disease.** 2nd Edn. By Charles F Farthing, Simon E Brown, Richard C D Staughton. Pp. 115. £16·00. Wolfe: London, 1988.

This is a well-illustrated short atlas of all the manifestations of AIDS. It has a good basic introduction on aetiology, immunology, and the origin and spectrum of the disease. A description of diseases in the different systems of the body follows. The section on eyes is rather brief. It finishes with some good advice on counselling of patients and prevention of transmission of the disease, with a particular note on cautions for doctors. I think this is a good book for those needing an overview of the disease in easily palatable form.

RONALD J MARSH

# NOTES

### Public health ophthalmology

A special master degree programme in preventive ophthalmology will again be offered during 1990–1 by the John Hopkins Medical Institutions under the auspices of its Dana Center for Preventive Ophthalmology, a World Health Organisation collaborating centre. The programme is designed for individuals interested in initiating, developing and providing leadership to national or regional blindness prevention activities and in conducting serious clinical epidemiological research. Five to 10 places are available for participants from developing and developed countries. A small stipend may be available to some participants to help defray living expenses. Further information from: Program Coordinator, Preventive Ophthalmology Program, DCPO, Wilmer Institute, Room 120, Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, Maryland 21205, USA.

### Preventive ophthalmology

The Dana Center for Preventive Ophthalmology of the Wilmer Eye Institute and Johns Hopkins School of Public Health will hold the third Master's Degree Program in Preventive Ophthalmology during the 1990–1 academic year. The course is designed to educate ophthalmologists from developed and developing countries in the application of epidemiological and other public health techniques to prepare them to assume leadership positions in clinical and public health research activities and prevention of blindness programmes. Some funds are available to help supplement the costs of participants from developing countries. Further information from PHO Program Coordinator, Dana Center for Preventive Ophthalmology, Wilmer Institute, Room 120, Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, MD 21205, USA.

### AIDS and loss of vision

The first International Conference on 'AIDS and vision loss' will be held on 25-26 January at the Marriott Hotel, San Francisco, USA. Further details from American Foundation for the Blind (Fay Ellis), 15 West 16 Street, New York NY 10011, USA (tel 212 620-2029).

# Two new titles from the BMJ's series of books of general interest by medical writers

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**Not a Moment to Lose** *by Sir David Smithers*

Sir David Smithers, former president of the British Institute of Radiology and of the Royal College of Radiologists, was for 30 years professor of radiotherapy at the Royal Marsden Hospital. But that is only half the story. He is also a man who believes that "one should aspire to be a realist but retain a sense of wonder, a rationalist who is prepared to jump to conclusions, and a critical visionary who remains sensible of the humour of the human situation". Recounting how he has lived according to these principles, David Smithers describes, in addition to his medical career, his experiences as a broadcaster, traveller, rose grower, and observer of human nature.

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**One Man's Medicine** *by Professor Archie Cochrane*

Archie Cochrane was one of Britain's most influential thinkers on health care and the quality of health services. His 30 years' association with the Rhondda Fach—and his work there on reducing the suffering inflicted on whole communities by pneumoconiosis—is almost legendary. Ironically, this was nearly overshadowed later in his life by the spectacular success of his Rock Carling monograph *Effectiveness and Efficiency*, which proved to be a seminal work and influenced thinking about the assessment of medical treatment and procedures throughout the world.

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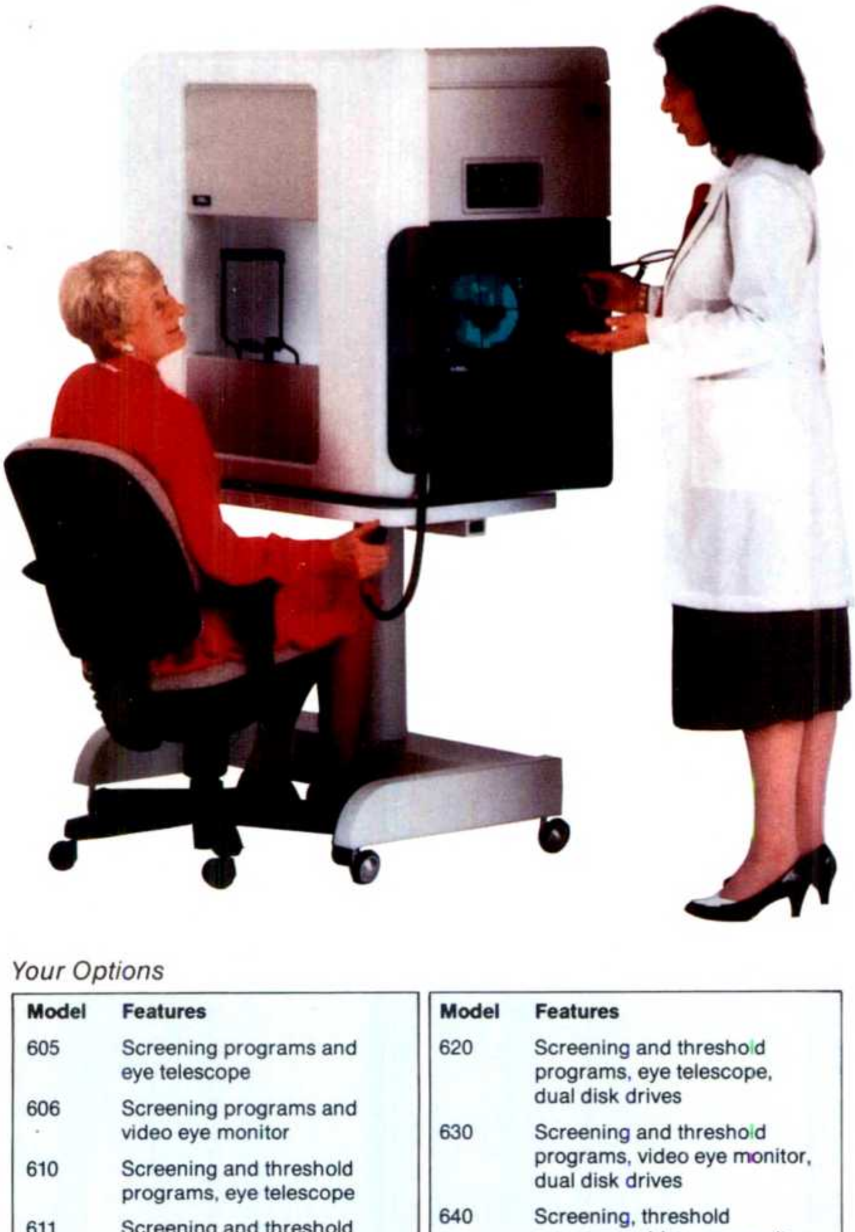

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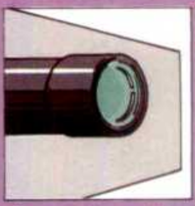

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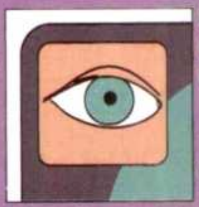

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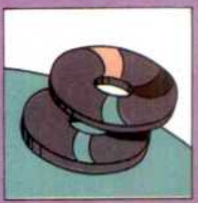

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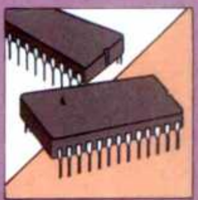

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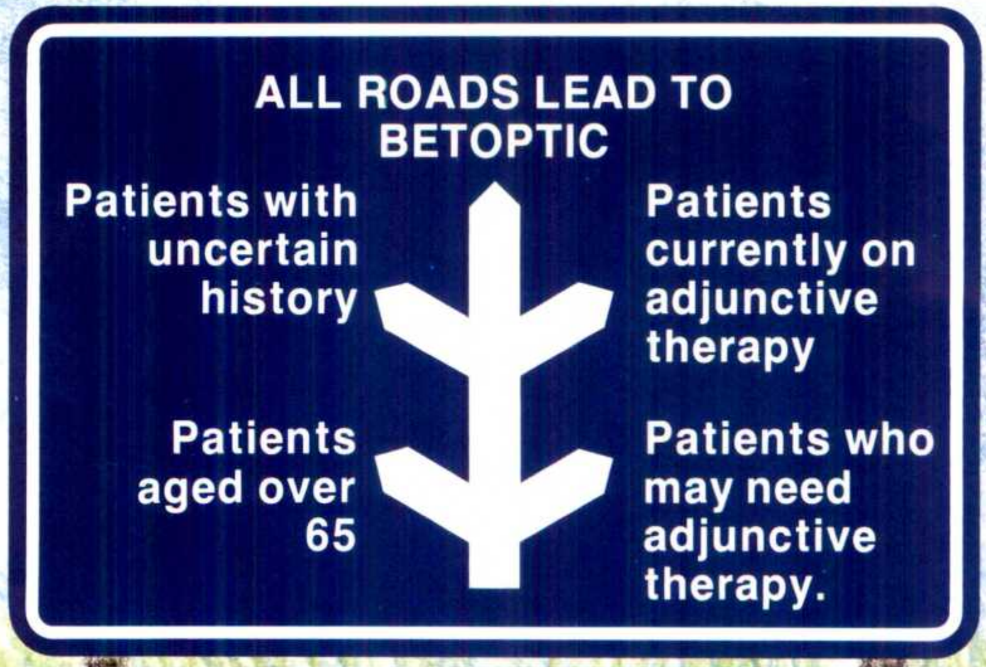
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*British Journal of Ophthalmology*, 1990, 74: 65

# *Editorial*

# The living contact lens

There are now a considerable number of ways of correcting visual defects due to errors of refraction. Most methods use glass or plastic outside the eye in the form of spectacles or contact lenses of various types. Like many things in life these have become so complicated of late, especially contact lenses, that the average ophthalmologist is hard put to it to keep up with the advances. In my own professional lifetime I have seen contact lenses change from large glass haptics to the present array of micro hard, daily wear soft, extended wear, gas permeable, disposable, varying water content types, and even bifocals, and no doubt, such is the speed of advance, I have probably missed out several others. Most optical appliances are supplied for errors of refraction of a non-pathological origin, moderate degrees of myopia, hypermetropia, astigmatism, and so on; but obviously some refractive errors are due to pathology, aphakia being the most obvious example.

In most developed countries some sort of insurance based system of health care exists, underwritten either by the state or by private insurers or a combination of the two. In all such systems there clearly has to be a distinction between what is allowable for benefit and what is not. In the UK system, for example, there has recently been a shift away from regarding spectacles for ordinary refractive errors as eligible for benefit (except for special categories of citizens), and contact lenses have never been regarded as eligible except in cases of definite pathology. The details may be different, but there must be some sort of similar regulations in all other countries with insurance based systems.

One could say therefore that optical appliances tend to occupy a sort of marginal status in the medical field. They are often prescribed by doctors and others for the relief of pathologically induced errors of refraction but far more often given for non-pathological errors. One could summarise the position by saying it may sometimes be borderline but nevertheless is reasonably well understood by all and sundry.

How does this compare with the correction of errors of refraction by surgical means, a recent innovation? Once again the methods can be applied to both pathological and non-pathological refractive errors. Not working in this field myself I have no idea how the insurance agencies overseeing health care in various countries support this form of surgery, but one would certainly expect it to be underwritten fully for pathological conditions, notably aphakia, though it has to be pointed out that the difference in cost between an operation and a contact lens or a pair of spectacles is certainly not negligible. But these are the problems of the health care underwriters, and I am not so sure that it is the responsibility of the medical profession to pontificate on this. One feels that the primary job of the doctor is to advise what ought to be done and if possible do it. The provision and allocation of funds is a political decision.

I was stimulated into these random thoughts about the correction of refractive errors by reading the paper by Halliday in this issue about the relatively new operation of epikeratophakia. Although the name implies correction of aphakia alone, the present paper reminds us that other refractive errors can respond to this technique also. The method has evolved from Barraquer's original operation of keratomileusis in which the patient's own cornea was partially removed, refashioned on a lathe, and then replaced. Derek Ainslie visited Barraquer in Bogota, brought the apparatus to Moorfields, and actually managed to carry out a number of the operations in the early 1970s. The results were quite encouraging, but the complexities of the procedure and the formidable nature of the hardware together with perhaps an unvoiced fear of the possibility of disaster in the event of something going wrong with the machinery, when a large portion of the patient's cornea was out of the eye, conspired to allow the method eventually to be given up, in this country at least.

Refractive surgery now comprises radial keratotomy (and variations), excimer laser refashioning and epikeratophakia, and doubtless in the not too distant future other methods. As in the case of optical appliances, some of the operations are going to be done for pathological refractive errors (particularly aphakia and high myopia) but many inevitably for non-pathological cases. This will tend to raise the sort of questions as have in the past been raised about the various methods of funding optical appliances and to what degree they should be considered 'medical' in any case, but with the extra dimension of ethical implications as well.

How far is it justified to cut tissues, particularly the tissues of the eye, where no disease is present but an improvement on what nature has provided is sought? Should we make a distinction between refractive surgery for pathological as opposed to non-pathological reasons, rather like the distinction between plastic surgery, with its long training and rigorous standards, and cosmetic surgery, which may have less exacting standards and a somewhat commercial background? Or should we mind our own business and leave the refractive surgeons to sort out their own arrangements? Probably the latter. I would hasten to point out that the article on epikeratophakia in no way comes into the 'cosmetic' category but is an honest and serious attempt to present the results of a single surgeon embarking on a novel surgical technique on almost exclusively pathological cases.

REDMOND SMITH

*British Journal of Ophthalmology*, 1990, 74: 66

# *Editorial*

## Paediatric cataract surgery

Although the popular image of ophthalmic surgery is that of a specialty in which procedures of great refinement and delicacy are carried out by virtuoso surgeons, many of our older operative techniques did not justify this image. In particular, the techniques which were formerly employed for the removal of congenital cataracts left much to be desired. In one version a needle was plunged into the lens, the only proviso being that complete transfixion was best avoided. During the course of the next few days the lens would further opacify and would also swell, with a considerable likelihood of secondary glaucoma. About one week after the initial needling, especially if glaucoma occurred, a keratome or small Graefe knife section would be made and an anterior chamber washout performed with varying degrees of efficacy – but always by a positive pressure technique without aspiration.

There were certain variations of this technique depending on the nature of the cataract. Quite frequently the second operation was omitted and the lens matter was allowed to become absorbed spontaneously. Later capsulotomy was usually required. Sometimes removal of lens matter was effected by 'curette evacuation', whereby a narrow elongated spoon was passed through the section into the pultaceous lens matter, which was then milked out of the eye by rubbing another curette or an iris repositor on the corneal surface, so that the lens matter was squeezed along the curette and out of the eye.

Subluxated lenses were looked at askance, and most surgeons tried to avoid getting involved. The prospect of massive vitreous loss without the benefit of adequate vitrectomy equipment (which had not yet been invented) was enough to deter most surgeons except the most adventurous, and the results of such surgery tended to be poor. Some good results were obtained, but the incidence of later complications, especially retinal detachment, was high. Anterior synechiae of lens capsule, iris, and even strands of vitreous were not uncommon and no doubt contributed to the poor prognosis.

Over the last few years the situation has changed dramatically, as illustrated by the paper in this month's issue by Hing and colleagues. Several reasons for the improvement can be given. The use of the surgical microscope is certainly one, the concept of simultaneous irrigation and aspiration is another, and the use of vitrectomy instruments is a third.

These advances have taken place within the clinical lifetime of most senior surgeons. I well remember, when visiting the Wilmer Institute in 1964, seeing David Paton, the then senior resident, doing what he called a 'push-pull' extraction on a congenital cataract. This was the method which foreshadowed the technique of simultaneous aspiration and infusion which is now the standard way of removing lens matter. Since appropriately fine tubing and cannulae were not available, the next best thing was to fill a hypodermic syringe with a suitable irrigating solution, fit a small needle, and, after introducing it into the eye, remove the lens matter by alternating suction and injection. The contents of the anterior chamber were gradually mixed with the contents of the syringe, and thus the lens matter was effectively diluted to the point where, after one or two changes of fluid in the syringe, it was virtually all eliminated. The worst feature of the operation from the surgeon's point of view was the surprisingly painful state of his or her metacarpophalangeal thumb joint after a 20-minute session of push-pull.

The incidence of retinal detachment cited in the 10-year series described in the present paper is only about 2·50%, a most creditable figure and surely due to the improved techniques. One notes in particular the lack of problems in the cases of lensectomy for ectopia lentis – a dramatic improvement on former times and almost certainly due to the better surgical techniques reducing the incidence of vitreous traction.

But problems still remain with these unfortunate children, the most obvious being amblyopia, and one feels that there must be an irreducible minimum incidence of this. Correction of the aphakia causes some controversy, and no doubt the experts in this field will continue to argue the merits of contact lenses versus intraocular implants. And, who knows, epikeratophakia may eventually also play a part.

REDMOND SMITH

ORIGINAL ARTICLES

# Epikeratophakia for aphakia, keratoconus, and myopia

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**Abstract**

**A series of 67 cases of epikeratophakia is presented with an average time from surgery of 12·2 months. For aphakia there was a delay in the recovery of vision, but by nine months 83% of 57 patients achieved an acuity equal to, or within 1 line of, the preoperative value. 57% were corrected to within 3 dioptres of emmetropia, but in the latter part of the series 75% were within this range. Astigmatism and reduced contrast sensitivity, especially in the presence of glare, were important complications. For keratoconus, 86% of seven patients with over two months of follow-up achieved a spectacle corrected acuity of 6/9 or better. One patient had surgery for myopia and obtained the desired refractive correction.**

Barraquer pioneered the use of the cryolathe in refractive surgery about 30 years ago. His technique of keratomileusis never gained widespread popularity. In contrast, epikeratophakia, introduced in 1980, has been taken up enthusiastically, especially in the United States. By 1986 over 1500 surgeons had been certified by Allergan Medical Optics (California, USA) to use their epikeratophakia lenses.

Keratomileusis failed to become widely accepted owing to problems with the technique. The range of refractive correction is limited to about 12 dioptres, and the surgical technique is invasive, with a lamellar disc of the patient's own cornea turned on a cryolathe to provide the refractive correction. Complications associated with keratomileusis include corneal perforation and cryolathe damage to the lamellar disc.

In contrast, epikeratophakia has a wide range of possible correction (up to about 30 dioptres of hyperopia or myopia), is largely non-invasive, and is usually reversible. Cryolathe lens manufacture may be centralised, allowing surgery to be performed by any corneal surgeon without requiring specialised equipment. Epikeratophakia with a plano lens may also be used to treat certain cases of keratoconus.

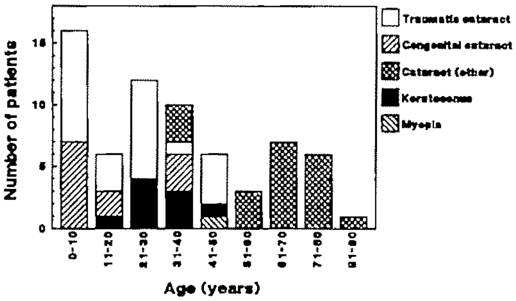

*Figure 1: Distribution of diagnosis with age of patient.*

Although there have been some case reports of failed epikeratophakia,[1-3] large published series (mostly from the United States) have generally concluded that epikeratophakia is a worthwhile procedure.[4-13] Despite this, the number of British surgeons performing the technique remains very small.

This paper presents a series of all the cases of epikeratophakia performed by the author to date and defines the categories of patients who may benefit from this procedure.

## Patients and methods

### SELECTION OF PATIENTS

Patients were referred to the corneal clinic at Moorfields Eye Hospital where they were assessed as potential candidates for surgery. Epikeratophakia was only considered when simpler alternatives such as spectacle or contact lens correction were considered inappropriate. Most patients had tried and failed contact lens wear, though in a few monocularly aphakic children, where contact lens correction was thought likely to fail, epikeratophakia was performed as the primary treatment.

Adult monocular aphakes suitable for surgery included those who had had previous intracapsular extraction on one eye followed by extracapsular extraction with intraocular implant on the fellow eye. Other potentially suitable patients included those with a history of uveitis who had had extracapsular surgery performed electively without lens implant and those who were aphakic following traumatic cataract. Bilateral aphakia was considered as an indication for epikeratophakia only in patients intolerant of a contact lens who preferred to remain uncorrected rather than wear spectacles.

Keratoconus patients whose corneal irregularity was such that spectacle correction was impossible, yet who had good acuity with a diagnostic contact lens, were considered ideal candidates for surgery. Patients with enough central scar to reduce contact lens acuity were treated by penetrating keratoplasty.

Patients who were equally myopic in each eye were not considered suitable candidates for surgery, as without exception they were managing with either contact lenses or spectacles. Monocular myopes who were uncorrected in their myopic eye were considered for surgery on the myopic eye, as were those with one eye markedly more myopic than the other.

In all cases the referring surgeon felt that the more invasive surgical alternatives, such as secondary intraocular lens implantation for aphakia, penetrating keratoplasty for keratoconus, or radial keratotomy for myopia, were contraindicated.

### LENS MANUFACTURE

For the first six procedures commercially produced lenses were imported from the United States. For the remainder lenses were manufactured by the author using donor corneas that had been stored either in K-Sol or McCarey-Kaufman storage medium.

A typical epikeratophakia lens has a central optical zone and a thin peripheral wing which is sutured to hold the lens in place. Most of the lenses were made with a specially developed cryolathe (Citycrown Sales, 14 Kempston Close, Gatehouse Way, Aylesbury, Buckinghamshire), which has a facility for automatically making a smooth transition between the radius of cut used for the optical zone and the radius used for the wing. Thirteen lenses were made on a lathe without this facility, and for these the transition between optical zone and wing was made manually. Alternatively, lenses were made with a single radius of cut, so that the optical zone in these extended to the edge of the lens.[14] Detailed descriptions of the formulae used to lathe the lenses has been published.[14-16]

### SURGICAL TECHNIQUE

The basic technique of epikeratophakia consists of initially removing corneal epithelium, then dissecting a peripheral pocket for the wing of the lens, which is then sutured in place. The exact technique employed evolved over this series.

Thorough removal of corneal epithelium is necessary so that there is no subsequent cellular proliferation at the interface between the epikeratophakia lens and host cornea. Epithelium peripheral to the lens should be left intact, as it is from this peripheral cornea that epithelial regeneration covers the epikeratophakia lens. Failure of prompt re-epithelialisation may be associated with melting of the lens and infective keratitis. For the initial seven cases absolute alcohol was used to drench the patient's cornea to aid removal of the epithelium. Unfortunately this proved to be associated with delay in subsequent re-epithelialisation. Subsequently a scalpel blade was used to remove epithelium, and the use of alcohol was confined to a final wipe with a barely damp swab, care being taken to avoid peripheral cornea.

The next step in the operation is to create a pocket for the insertion of the wing of the lens. In most cases a 7 or 7·5 mm diameter Hessburg-Baron suction trephine was used to make a partial thickness trephination to a depth of about 180 μm. A 21 gauge needle, bent to 90° 2 mm from the end, was then used to dissect a pocket, parallel to the corneal surface, from the base of the partial thickness trephination extending peripherally. In the initial four cases an annular wedge of cornea was removed from the inside edge of the trephination. In 10 cases no trephine was used. For these cases after circular mark had been made on the cornea an annulus (of Bowman's layer and underlying corneal stroma) was excised with a razor blade and Paufique's knife. This approach was used for some of the 13 lenses made without a peripheral wing, which were simply sewn on to the surface of the cornea, allowing the 'bare area' of the annulus to approximate the deep surface of the lens.[14]

The final part of the operation is to fix the lens in place. In all but two cases this was done with 10-0 monofilament sutures. Initially 16 sutures were used, but it soon became apparent that eight sutures were usually sufficient. Exceptionally up to 24 sutures were used for those lenses made without a peripheral wing that were sewn on to the surface of the cornea. In two cases a fibrin glue (Tisseal; Immuno Ltd, Sevenoaks, Kent) was used to fix the lens in place of sutures. For aphakia and myopia the sutures were not tied tightly. For keratoconus very tight sutures were tied while an assistant pressed firmly to reduce the ectatic cornea.

For all the keratoconus cases the sutures were

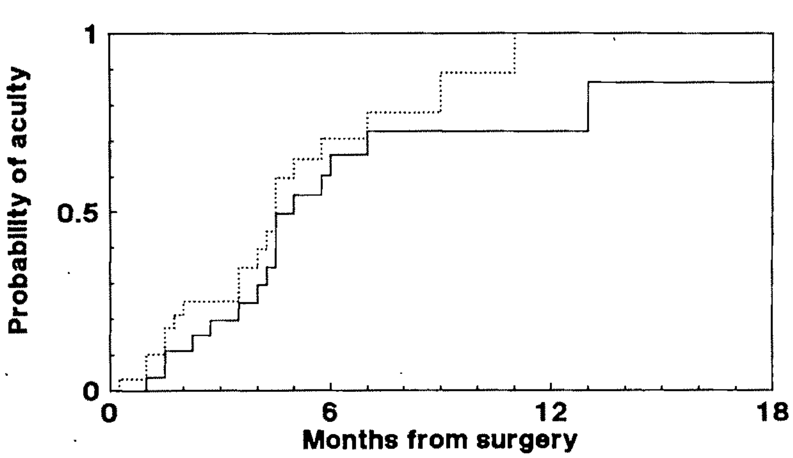

*Figure 2: The probability of an aphakic patient achieving a visual acuity of 6/12 (dotted line) and 6/9 (solid line) is plotted against time for surgery.*

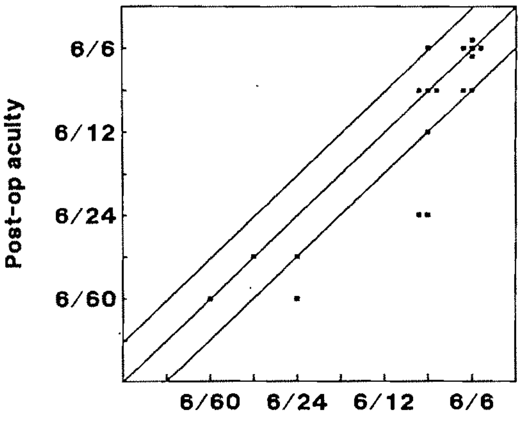

*Figure 3: Scattergram showing postoperative acuity against preoperative acuity for all aphakic patients with at least nine months of follow-up.*

tied with the help of an operative placido disc, sutures being added or removed as dictated by the symmetry of the reflex in an attempt to reduce induced astigmatism. This technique was also used for the most recent aphakic cases.

In all cases the operation was completed with a subconjunctival injection of antibiotic and the eye padded until the next morning. In 17 cases early in the series a bandage contact lens (75% water content, back central optic radius 9 mm, overall diameter 15 mm) was used until the epithelium had regenerated to cover the cornea. Subsequently eyes have been left to epithelialise without the use of contact lenses, eye pads, or lid sutures.[17]

Postoperatively topical antibiotic and weak steroid drops were used, usually three times a day, for about eight weeks. During this time sutures were removed from the aphakic and myopic cases, but for keratoconus the sutures were left in place unless they became loose or were inducing astigmatism. Patients were refracted at regular intervals, starting as soon as the epikeratophakia lens had cleared sufficiently. To provide more information on visual function, selected patients had contrast sensitivity measurements in both the operated eye and in the fellow, normal eye. A computer controlled system was used with sinusoidal gratings displayed on a television monitor with an average luminance of 14 $cd/m^2$. As some patients had reported a reduction in vision in bright light, the measurements of contrast sensitivity were repeated in the presence of a glare source of luminance 300 $cd/m^2$ (Brightness Acuity Tester; Mentor Inc, USA).

## Results

From October 1986 to May 1989, 67 epikeratophakia procedures were performed: 25 were for traumatic aphakia, 16 for aphakia following intracapsular cataract extraction, 12 for aphakia following congenital cataract extraction, 4 for aphakia following extracapsular cataract extraction, 9 for keratoconus, and 1 for myopia. The average age of the patients was 34 years (range 1 to 82). Figure 1 shows in detail the distribution of age and diagnosis. The average time from surgery was 12·2 months (range 1 to 32).

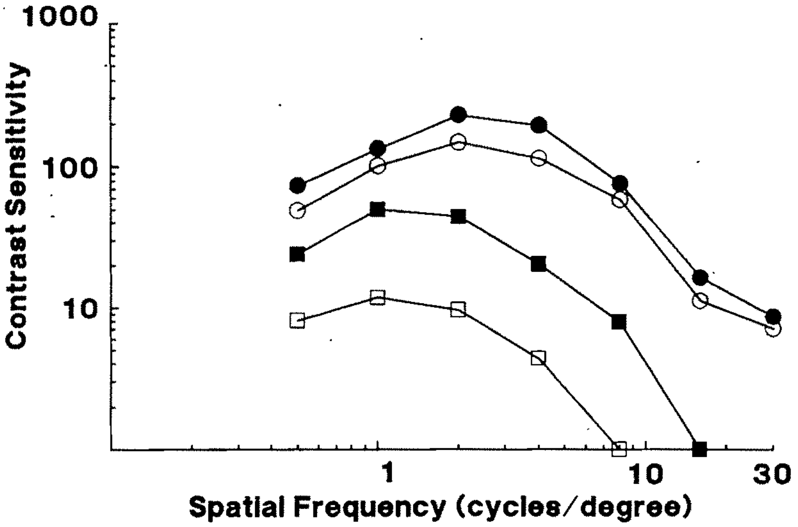

*Figure 4: Contrast sensitivity is plotted against spatial frequency for a patient following aphakia epikeratophakia. Squares represent the epikeratophakia eye; circles represent the normal, fellow eye. Filled symbols indicate testing under normal conditions; open symbols indicate testing in the presence of glare.*

Most of the patients had an uneventful postoperative course, with rapid re-epithelialisation of the epikeratophakia lens and with steadily improving lens clarity paralleled by improvement in corrected visual acuity. Loosening of sutures was a very common complication, and these were removed as required.

The time taken for complete epithelialisation of 10 consecutive patients managed with a bandage contact lens was compared with the time taken by the next 10 patients managed without a contact lens. The contact lens group took an average of 3·9 days to complete epithelialisation (range 3 to 5 days), whereas the untreated group took 3·8 days (range 3 to 5 days). Re-epithelialisation when successful was complete by seven days postoperatively.

### APHAKIA – VISUAL RESULT

Recovery of visual acuity after epikeratophakia is known to be slow. In this series the visual acuity of individual patients steadily improved over periods as long as a year after surgery. Twenty-five cases of epikeratophakia for aphakia with a preoperative acuity of at least 6/9 were studied in detail to analyse this recovery of acuity. The average age in this group was 47 years (range 9–82). Survival (Kaplan-Meir type) analysis was used to plot the probability of achieving acuities of 6/12 and 6/9 at a given time after surgery (Fig 2). This shows that it took 4·4 months for 50% of cases to reach an acuity of 6/12 and 4·8 months to reach 6/9.

Figure 3 is a scattergram plotting postoperative against preoperative acuity for all aphakic cases with at least nine months of follow-up. Of the 18 cases plotted 11 (61%) achieved their preoperative acuity and 15 (83%) achieved an acuity within one line of the preoperative value. All of the three cases that failed to reach this level of acuity had clinically clear epikeratophakia lenses. One of these cases had developed disciform senile macular degeneration, one had a high cylinder (7 dioptres), and the other had no apparent reason for poor acuity.

Contrast sensitivity was measured in four patients. In every case the Snellen acuity in the epikeratophakic eye was 6/9 or better, and this was not reduced by the presence of the glare source. Figure 4 shows a typical result. In the absence of glare the contrast sensitivity of the epikeratophakic eye was approximately 0·75 log units worse than the phakic, fellow eye. In the presence of glare the relative deficit in the epikeratophakic eye increased to over 1 log unit. Full details of the contrast sensitivity measurements in these patients have been published elsewhere.[18]

### APHAKIA – REFRACTIVE RESULT

Figure 5 is a scattergram showing correction achieved (spherical equivalent, dioptres) against preoperative refraction. 57% of patients were corrected within 3 dioptres of the desired value. The remaining 43% were outside this range and

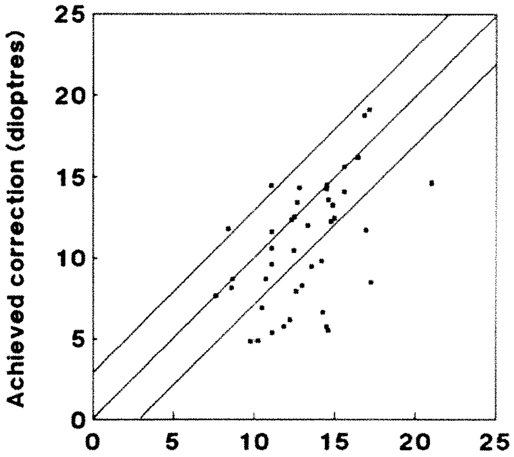

*Figure 5: Scattergram showing achieved refractive change against preoperative refraction for aphakic patients.*

thus, in general, unable to be satisfactorily corrected with spectacles. Results improved considerably as formulae for lathing were modified over the period of this study. For the first 12 lenses made only 25% were within 3 dioptres of the desired correction, whereas for the most recent 12 cases 75% were within this range.

Postoperative astigmatism varied from 0 to 8 dioptres. The average magnitude was 2·5 dioptres, with 43% of cases having a cylinder of over 3 dioptres. This problem has shown a tendency to improve over the duration of the study: 50% of the first 12 cases had a cylinder of over 3 dioptres, whereas for the most recent 12 cases, only 25% had cylinders over this value.

### PAEDIATRIC APHAKIA

Sixteen cases of aphakic epikeratophakia were performed on children aged 10 years or under. Refractive and visual results, where available, have been included in Figures 2, 3, and 5. Table 1 provides more details. Nine out of 13 eyes refracted (69%), were corrected to within 3 dioptres of emmetropia. Two children in this study were seriously undercorrected. Patient 6 had a microphthalmic eye and congenital cataract. Lensectomy was performed at age 1 month, but contact lens wear proved increasingly difficult so epikeratophakia was performed at the age of 4 years. A correction of 32 dioptres was needed, but only half of this was achieved. Nevertheless, with amblyopia therapy vision in this eye has improved to 6/60, and the patient is now 6½ years old. Patient 13 received only about 60% of the desired correction, and epikeratophakia may be repeated. Postoperative binocular function has been recorded in two cases; patient 2 can fuse images on the synoptophore over a limited range, and patient 14 achieves rudimentary stereopsis. Patient 15 has had his epikeratophakia lens removed as detailed below.

TABLE I *Results in paediatric aphakia*

| *Patient no.* | *Age (years)* | *Diagnosis* | *Follow-up (months)* | *Preop. acuity* | *Postop. acuity* | *Postop. refraction* |
|---|---|---|---|---|---|---|
| 1 | 1 | C (U) | 7 | NK | NK | Approx plano |
| 2 | 3 | T | 7 | NK | 6/18 | 5·00/−1·00×140 |
| 3 | 3 | T | 1 | NK | NK | NR |
| 4 | 3 | T | 3 | NK | NK | 2·00 sph |
| 5 | 3 | T | 1 | NK | NK | NR |
| 6 | 4 | C (U, M) | 8 | CF | 6/60 | 16·00/−2·00×90 |
| 7 | 5 | T | 5 | NK | 6/18 | −2·00 sph |
| 8 | 5 | T | 1 | NK | NK | 6·00 sph |
| 9 | 5 | C (U) | 3 | CF | CF | Approx plano |
| 10 (left eye) | 7 | C (B) | 14 | 6/24 | 6/36 | 2·50/−4·50×180 |
| 10 (right eye) | 7 | C (B) | 5 | 6/60 | 6/60 | 2·00/−4·00×130 |
| 11 | 7 | T | 2 | 6/12 | 6/24 | 2·50/−6·00×130 |
| 12 | 8 | C (B) | 22 | 6/60 | 6/60 | −2·00 sph |
| 13 | 8 | T | 5 | 6/6 | 6/12 | +10·00/−3·25×180 |
| 14 | 9 | T | 6 | 6/6 | 6/6 | +1·00/−1·50×25 |
| 15 | 10 | C (B) | 1 | 6/18 | NK | NR |

C=congenital cataract. U=unilateral. B=bilateral. T=unilateral traumatic cataract. M=microphthalmic eye. CF=counting fingers. NK=acuity not known. NR=not refracted.

### APHAKIA – COMPLICATIONS

Both epikeratophakia lenses that were glued in place became dislodged by the second postoperative day. Both lenses were removed, and new lenses were sutured in place without further complication.

Two cases failed to epithelialise postoperatively despite intensive inpatient management including the use of bandage contact lenses, eye pads, and lid taping. In both cases it proved necessary to remove the epikeratophakia lens about four weeks after surgery. In one case there was no obvious reason, but the other patient (number 15 in the paediatric aphakia group) had severe icthyosis, which may have been contributory.

Two cases had epithelial breakdowns after uncomplicated initial epithelialisation. The first developed a linear defect two months after surgery. This was treated with topical antibiotics only, and healed within one week. The second patient had a larger area of defect that occurred at two weeks. This was managed with a bandage contact lens. This defect recurred at three months and was again successfully managed with a contact lens, leaving a clear epikeratophakia lens. One patient has had recurrent filamentary keratitis that has required topical acetyl cysteine 5%; the lens has remained clear.

Late lens removal, between six and 13 months after surgery, has been required in eight cases. Under topical anaesthesia the wing of the lens was dissected out of its pocket, and then the lens peeled away easily from the host cornea. In all these patients re-epithelialisation was without problems. Five lenses were removed for incorrect refractive result (an average of 5·8 dioptres of undercorrection). One lens was removed for high astigmatism (7 dioptres), one when the penetrating keratoplasty that it was sewn over failed, and one removed when visual

TABLE II *Results in keratoconus*

| *Patient no.* | *Follow-up (months)* | *Preop. acuity* | *Postop. acuity* | *Postop refraction* |
|---|---|---|---|---|
| 1 | 15 | CF | 6/9 | 1·00/−2·00×142 |
| 2 | 11 | 6/18 | 6/9 | 2·00/−2·00×20 |
| 3* | 9 | CF | 6/12 | −3·50/−11·00×50 |
| 4 | 9 | 6/60 | 6/6 | −0·50/−2·00×90 |
| 5 | 5 | 6/24 | 6/9 | −8·00/−2·25×70 |
| 6 | 3 | CF | 6/9 | −11·00/−2·00×50 |
| 7 | 3 | 6/60 | 6/9 | 0·50/−3·50×107 |
| 8 | 1 | 6/36 |  | NR |
| 9 | 1 | CF |  | NR |

CF=counting fingers. NR=not refracted.
*Patient 3 had 2 dioptres of astigmatism three months after surgery, 5 dioptres at six months and finally, 11 dioptres at eight months. At this time the epikeratophakia lens was removed and penetrating keratoplasty performed.

acuity failed to improve beyond 6/24 despite a preoperative acuity of 6/9. Four patients have since received a secondary lens implant, two have had repeat epikeratophakia, and two have not had further surgery.

Interface opacities have not been an important problem. In five cases typical small, midperipheral, putty grey areas have appeared at the interface. All these patients have now been followed up for at least six months, and the areas of presumed epithelial cell proliferation do not appear to be progressing and none impinge on the visual axis.

### KERATOCONUS

Table 2 shows the results for each keratoconus patient. All patients were intolerant of contact lenses, and the preoperative acuity shown is the best that was possible with spectacle correction. Six out of seven patients (86%) with more than two months' follow-up achieved a good result with spectacle corrected acuity of 6/9 or better. The remaining patient achieved 6/12 but with very high cylinder and required penetrating keratoplasty.

### MYOPIA

The single myopic patient treated has a preoperative refraction of −15 dioptres in the right eye (acuity 6/9) and −30 dioptres in the left (acuity 6/36). Epikeratophakia was performed on the left eye, aiming to balance its refraction to that of the right eye. After one month of follow-up the acuity in the left eye was 6/60 with a correction of −15 dioptres.

## Discussion

The improvement in the results over the series, in terms of spherical error and astigmatism, represents a learning curve for both lens manufacture and surgical technique.

Twelve (21%) of the aphakic lenses were removed. This is a rather higher proportion than found in the other series where overall 6% of over 900 were removed.[4 7-9] Seven of the 12 removals in this series may be attributed to the learning curve; five were removed for serious undercorrection, and two were removed following the use of fibrin glue. One lens failed because of underlying graft failure.

Results in paediatric aphakia are difficult to compare from study to study. Paediatric patients form a very diverse group with varying ages, often unknown duration of cataract, and varying times from cataract surgery to correction of aphakia. Maintaining full time contact lens correction is difficult, and the delay in restoring clarity after epikeratophakia may be important. Refraction and acuity are difficult to assess, and problems in maintaining occlusion limit the results of amblyopia therapy. Babies under the age of 1 year were not considered for epikeratophakia in this study, as it has been found that in this age group there is a marked shift to myopia as the eye grows.[19] Children beyond the age when amblyopia is a problem who suffer traumatic cataract often choose not to persevere with contact lens correction, lose binocular function, and their vision becomes divergent. The presence or rudimentary stereopsis in paediatric patient 14 is therefore encouraging.

Postoperative epithelialisation appeared to be much faster in this series than in many others. Apart from the two cases where primary re-epithelialisation failed, every eye was fully epithelialised by seven days, with an average time of less than four days. In contrast other reports have variously found only 75% epithelialised by one week,[20] average times to re-epithelialisation of 13 days,[21] and 15% of cases taking more than two weeks.[12] The explanation for this and for the fact that in this series routine use of bandage contact lenses, eye pads, or lid sutures did not seem necessary, may relate to the manufacturing and surgical techniques used. Most lenses used in this series were not lyophilised. Lyophilisation is needed to ship lenses, but the process inflicts additional damage to Bowman's layer of the lens[22] and so may inhibit re-epithelialisation. The surgical technique used prevented alcohol from damaging peripheral cornea which may otherwise have retarded re-epithelialisation.

The time course for the recovery of visual acuity has not previously been reported with survival (Kaplan-Meir type) analysis. Reports agree, however, that many months may be required for recovery of visual acuity after surgery.[4 10 12] The 83% of patients in this study who achieved an acuity within 1 Snellen line of the preoperative value by nine months is very close to the 82% that achieved this level more than three months after suture removal in a study of 150 patients.[4]

The reduction found in contrast sensitivity, especially in the presence of glare, may explain the subjective experience of some patients that their epikeratophakic eye does not provide as good vision as their fellow eye. The reduction in contrast sensitivity has been confirmed elsewhere,[23] and comparison has been made with contrast sensitivity of phakic and contact lens corrected eyes.[18]

The single case of myopia resulted in the desired refractive correction, and the patient is delighted with the result. The largest reported series of myopic epikeratophakia found that 58% of patients were corrected to within 20% of the required refraction.[5] In comparison with the corresponding series of adult aphakia, it was necessary to remove over twice as many lenses in the myopic group. Serious overcorrection of the refractive error seems to be more of a problem with myopic than with aphakic corrections.[24] Myopic lenses are no longer supplied by Allergan Medical Optics, who are now concentrating research on other means of correcting myopia.[20]

The results from this study are broadly similar to those reported elsewhere. The main difference is that patients treated in the early part of this study had relatively inaccurate refractive corrections. Improved lathing formulae later eliminated this difference.

Epikeratophakia for aphakia is a far from perfect operation. The majority of patients may expect to need spectacle overcorrection, and about one-quarter will be more than 3 dioptres from the desired refraction. Furthermore the quality of vision is suboptimal, with reduced contrast sensitivity especially in the presence of glare. For keratoconus the results so far seem highly encouraging. Patients have had restoration of good spectacle acuity without the need for penetrating keratoplasty. There are not enough myopic patients in this series to enable a firm conclusion to be reached, but the solitary case treated has done well.

Selection of patients for epikeratophakia is, as with any operation, dependent on balancing the probable benefits with the potential complications. This study has confirmed that epikeratophakia is a very safe and mostly reversible procedure.

For aphakia epikeratophakia is indicated where spectacle or contact lens correction is impracticable and where a secondary implant is either impossible, such as following severe anterior segment trauma, or highly inadvisable, such as in children. Where a secondary anterior chamber implant is technically feasible, a decision must be made in each individual case where the increased safety of epikeratophakia over intraocular surgery justifies the relatively poor accuracy of refractive result, reduced contrast sensitivity, and delay in visual recovery.

For keratoconus the results so far favour epikeratophakia as the preferred management of patients with poor spectacle acuity and contact lens intolerance who have good diagnostic contact lens acuity. The more invasive penetrating keratoplasty may be performed if epikeratophakia subsequently fails. Epikeratophakia is a potentially valuable addition to the armamentarium of the ophthalmic surgeon. For carefully selected patients it can provide worthwhile visual improvement without the risk of intraocular surgery.

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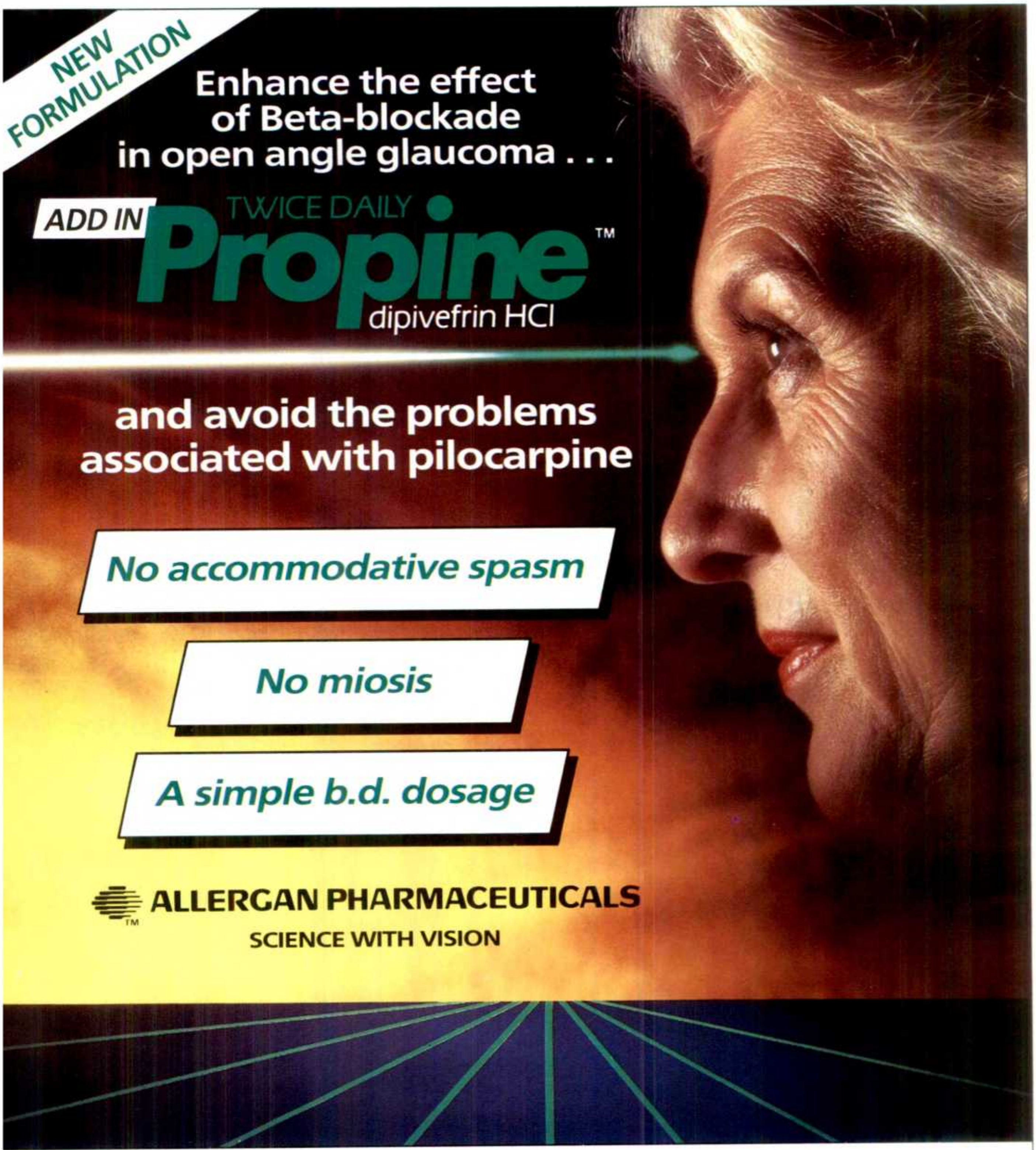

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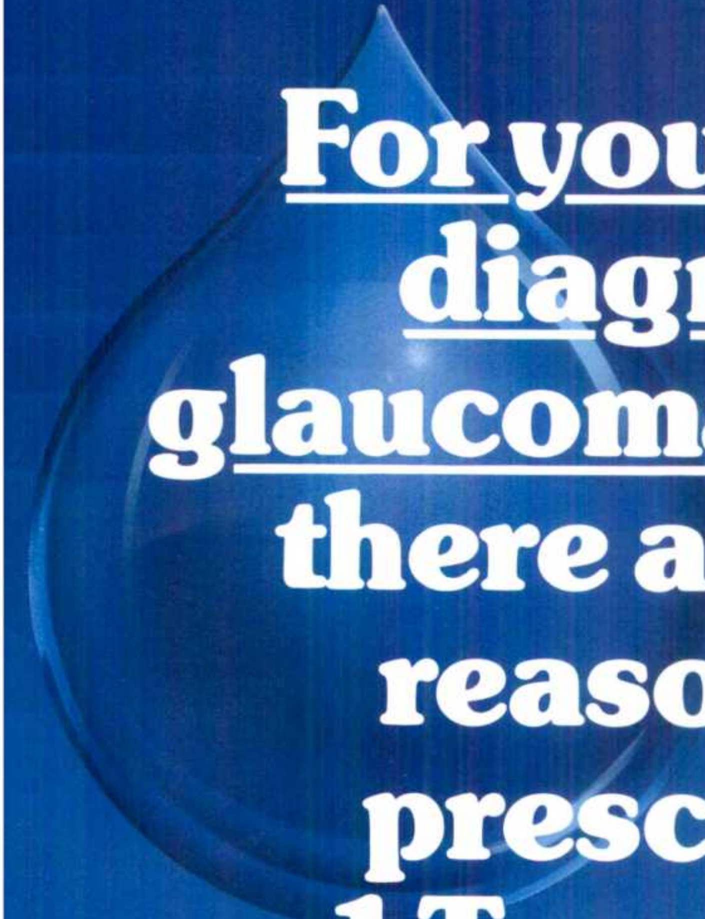

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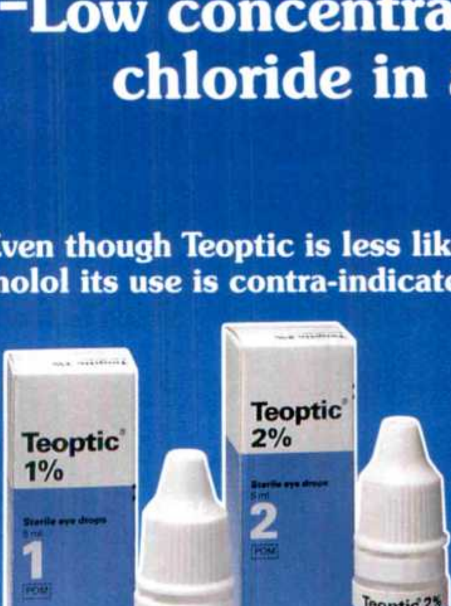

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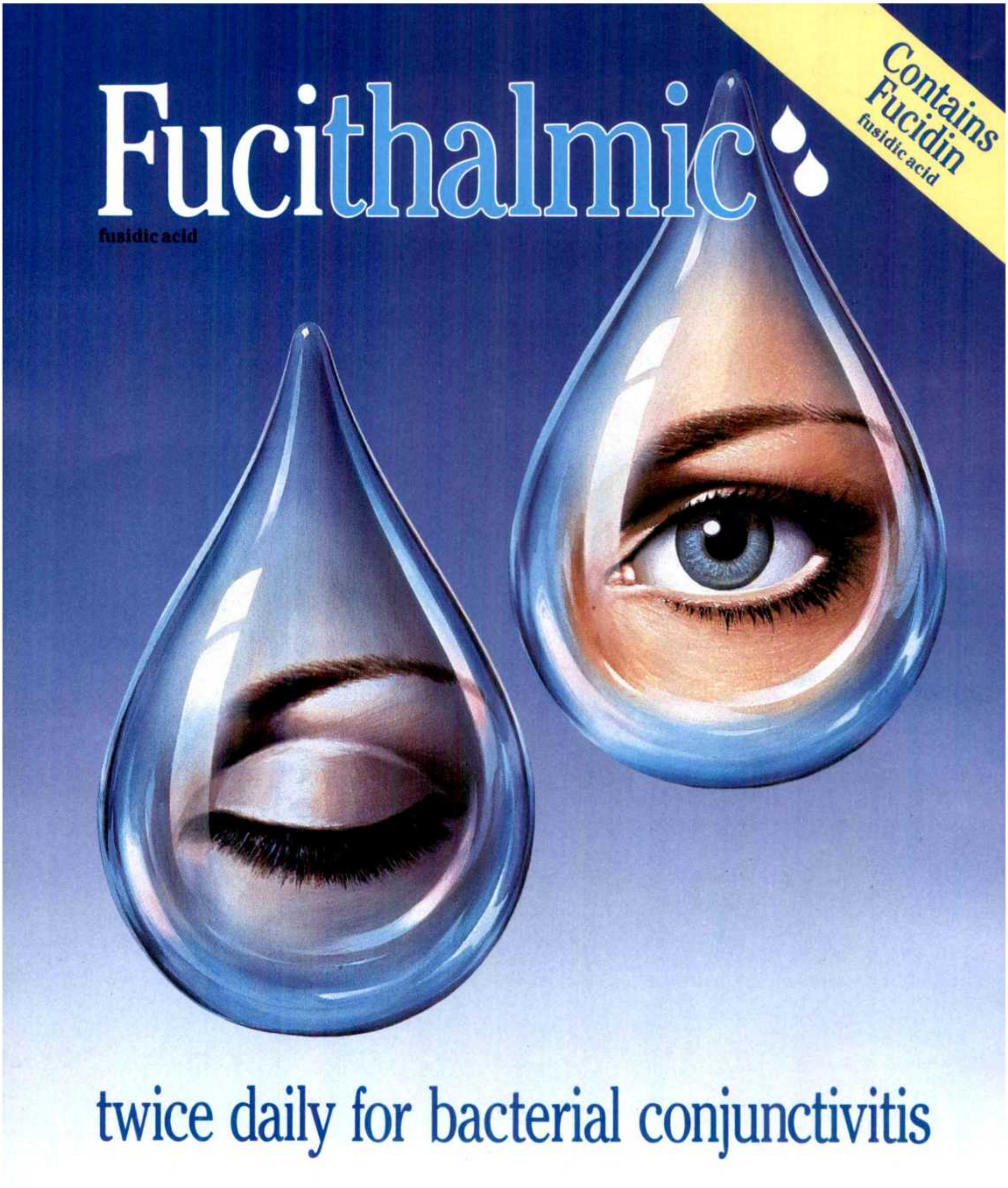
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# Lens surgery in infancy and childhood

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## Abstract

**The medical records of 224 children who had lens surgery performed at the Hospital for Sick Children during the 10-year period 1978–88 were reviewed. There were 12 children with ectopia lentis; these patients achieved a mean postoperative acuity of 0·68 (6/8·8), and no operative or postoperative complications were noted. Two hundred and twelve children had lens surgery for cataracts or for retrolental abnormalities with a clear lens. Children with bilateral congenital cataracts achieved a mean acuity in the better eye of 0·32 (6/18). In a series of carefully controlled unilateral congenital cataracts the visual results were poor. The postoperative complication rate for cataract and clear lens surgery was 4·6%. Because visual results are probably better with early surgery we emphasise that every newborn baby should be tested for media opacities.**

The commonest reason for operating on the lens in infancy and childhood is to remove a cataract, but sometimes a clear lens is removed if the anterior chamber is flat or shallow and glaucoma is present or threatening – for example, in some cases of persistent hyperplastic primary vitreous (PHPV) and retrolental fibroplasia (RLF). The other reason for operating on the lens in childhood is dislocation of the lens.

TABLE I *Type of surgery in 212 patients*

| | |
|---|---|
| Lensectomy | |
| Bilateral | 80 patients |
| Unilateral | 52 patients |
| Lensectomy in one eye aspiration in the other | 25 patients |
| Total | 237 procedures |
| Aspiration | |
| Bilateral | 29 patients |
| Unilateral | 26 patients |
| Aspiration in one eye lensectomy in the other | 25 patients |
| Total | 109 procedures |
| Total number of primary procedures | 346 |

TABLE II *Mean age at presentation in congenital cataract*

| | | *Number* |
|---|---|---|
| Bilateral | 4·5 months (range 9 days–19 months) | 87 |
| Unilateral | 10·7 months (range 1–26 months) | 31 |

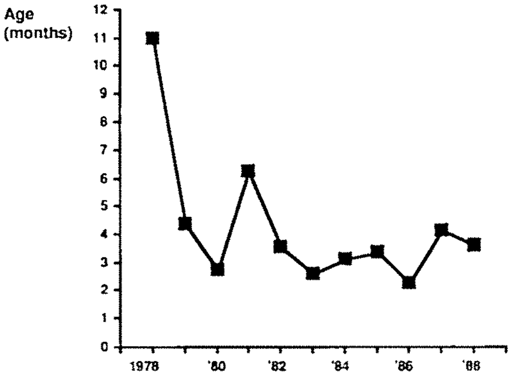

*Figure 1: Mean age at presentation to the clinic of infants with bilateral congenital cataract between 1978 and 1988.*

In this paper we report the results of a retrospective study of lens surgery at the Hospital for Sick Children and discuss the management.

## Material and methods

The medical records of children who underwent lens surgery at our institution between July 1978 and June 1988 were examined. Most cases were under regular review by us, others were reviewed specially, and information was requested from the patient's current ophthalmologist where one could be identified.

The visual acuities quoted are Snellen line acuities; as they were tested at various distances, they have been converted to decimal fractions and averaged. Children who were unable to do the Snellen vision test reliably were not included in the averaged visual results.

## Results

The records of 224 children were available. Of these, 12 had surgery for ectopia lentis and the rest had either cataracts or clear lenses associated with retrolental abnormalities.

### ECTOPIA LENTIS

Of the 12 children six were cases of simple ectopia lentis, four had Marfan's syndrome (three with a positive family history), and two children had homocystinuria (one with an affected sibling). Most of the children presented because of poor vision, but one child presented because the parents had noted iridodonesis. The average preoperative vision was 0·15 (6/40) (20 eyes). Two children had unilateral surgery and the rest bilateral. All children had a lensectomy via a corneal incision as the initial procedure. The average age at surgery was 69 months. Three children had second surgical procedures, which were all divisions of vitreous strands and performed within three months of the initial procedure.

The average postoperative vision was 0·68 (6/8·8) (16 eyes). In an average follow-up period of 22·4 months (range 3–65 months) there have been no operative or postoperative complications in these children.

### CATARACT AND CLEAR LENS SURGERY

*Follow-up.* The mean follow-up time for the whole group was 36 months (range 2 weeks to 10·3 years). The mean follow-up times for specific groups are given with the visual acuity results.

*Type of surgery.* A total of 346 primary lens operations were performed. These were either a lensectomy or lens aspiration. Lensectomy involved the removal of the whole lens, complete with anterior and posterior capsules and anterior vitreous with an aspirating/cutting machine via a corneal wound, and a separate infusion port or irrigating cystitome. Lens aspiration comprised the removal of the anterior lens capsule, all lens cortex and nucleus, leaving the posterior capsule intact. Twenty five children with bilateral cataracts had an aspiration of one lens and a lensectomy performed in the other eye (Table I). Children over 18 months usually had lens aspirations; infants with congenital cataracts had either lensectomies or aspirations, and all those with retrolental abnormalities had lensectomies.

*Age at presentation.* Bilateral congenital cataracts presented earlier than unilateral abnormalities (Table II). The graph (Fig 1) shows that among babies with dense bilateral congenital cataracts presenting from within the UK there has been a slight trend towards earlier presentation. The years with the earliest average age of presentation were 1983 and 1986. The time between when symptoms were first noticed and presentation at hospital was at a minimum in 1983 (1·25 months).

The mean age at presentation of babies with a family history of cataracts was 4·1 months (17 children). The average age at presentation of those without a family history was 4·6 months (70 children).

*Reasons for presentation.* The primary symptom noted in each case is given in Table III. Poor vision was the commonest reason for presentation, especially in older children. Babies with congenital cataract tended to present with leucocoria or nystagmus. Thirty eight children's lens abnormalities were detected by a routine test; in some this was because cataracts were suspected (for example, in Down's syndrome or family history of cataracts), but in 26 cases the cataracts were a surprise finding at a neonatal check, school test, or admission to hospital for an unrelated condition.

*Presenting signs.* Nystagmus or random eye movements were the commonest presenting signs (Table IV). Microphthalmos varied in degree from quite severe forms with horizontal corneal diameters often less than 8 mm associated with PHPV to eyes just less than normal size. Twenty seven children had shallow or flat anterior chambers. These are the cases of PHPV, RLF, and other retrolental abnormalities. Esotropia was commoner in the congenital cataract group, while exotropia was commoner in the juvenile age group.

*Diagnosis.* In Table V 'simple' refers to an uncomplicated cataract in an otherwise normal, except perhaps microphthalmic, eye. In 'congenital' cases the cataracts were severe enough to cause visual deprivation from birth. In 'infantile' cases the visual deprivation occurred later than this but before the second birthday. These children had apparently normal fixation and no nystagmus in early infancy. In 'juvenile' cases the onset of the apparent visual deprivation occurred after the second birthday.

TABLE V *Diagnosis in 212 children with cataracts and retrolental abnormalities*

| | |
|---|---|
| Simple bilateral congenital cataracts | 59 |
| Simple unilateral congenital cataract | 13 |
| Simple infantile cataracts | 15 |
| Simple juvenile cataracts | 29 |
| Rubella syndrome | 21 |
| Trauma | 12 |
| Retrolental fibroplasia | 12 |
| Severe PHPV | 9 |
| Down's syndrome | 9 |
| Retinal dysplasia | 8 |
| Uveitis | 6 |
| Anterior chamber cleavage syndrome | 4 |
| Norrie's disease | 2 |
| Cerebro-oculo-facial-skeletal syndrome | 2 |
| Lowe's syndrome | 2 |
| Systemic steroid induced | 1 |
| Retinal dystrophy | 1 |
| Diabetes | 1 |
| Radiation | 1 |
| Galactosaemia | 1 |
| Diagnosis uncertain | 4 |

TABLE VI *Positive family history*

| | |
|---|---|
| Autosomal dominant | 28 |
| Probable autosomal recessive | 12 |
| X-linked recessive (Norrie's) | 2 |

TABLE VII *Positive family history*

| | | % |
|---|---|---|
| Simple bilateral congenital | 20/59 | 34 |
| Infantile | 2/15 | 13 |
| Juvenile | 9/29 | 31 |

TABLE III *Reason for presentation in 212 children with cataract or retrolental abnormalities*

| | |
|---|---|
| Poor vision | 45 |
| Routine test | 38 |
| Leucocoria | 31 |
| Squint | 26 |
| Nystagmus | 19 |
| Trauma | 12 |
| Painful glaucoma | 4 |
| Microphthalmos | 4 |
| Photophobia | 3 |
| Combination of above | 40 |

TABLE IV *Presenting signs in 212 children with cataract and retrolental abnormalities*

| | |
|---|---|
| Nystagmus/random eye movements | 79 |
| Esotropia | 41 |
| Microphthalmos | 40 |
| Shallow/flat anterior chamber | 27 |
| Exotropia | 20 |
| Retrolental mass (9 ROP) | 11 |
| Retinopathy (6 rubella) | 7 |
| Band keratopathy | 4 |
| Posterior lenticonus | 4 |
| Opaque cornea | 3 |

Four of the cases of uveitis and the systemic steroid induced case had juvenile rheumatoid arthritis. The child with the radiation induced cataract had been treated for leukaemia. Overall, only 56% of the cases were simple cataracts.

*Family history.* Table VI shows the inheritance pattern in 42 cases (of 212) in which there was a positive family history. There was a negative family history in 162 cases and in eight the family history was not recorded. In the probable autosomal recessive group the parents were first cousins in seven cases, in another three cases there was no consanguinity but at least two siblings of different sexes had cataracts, and two occurred in known autosomal recessive syndromes. All the cases with a positive family history were bilateral. The percentage of simple cases with a positive family history is shown in Table VII.

*Indications for surgery.* 86% of the children were operated on to improve vision (Table VIII), though some had a poor visual prognosis from the outset – for example, because of retinal dystrophy, Peter's anomaly. Twenty cases underwent clear lens surgery to treat or prevent angle closure glaucoma. In 10 cases the leucocoria was a cosmetic problem.

*Operative complications.* The operative complications are set out in Table IX. Vitreous

TABLE VIII *Indications for surgery*

| | *Patients* |
|---|---|
| To improve vision | 182 |
| To avoid glaucoma | 14 |
| To treat glaucoma | 6 |
| Cosmetic | 10 |
| Total | 212 |

TABLE IX *Operative complications*

| | *Eyes* |
|---|---|
| Vitreous haemorrhage | 10 |
| Rupture of the posterior capsule | 2 |
| Choroidal effusion | 1 |
| Wrong irrigating fluid | 1 |

haemorrhage was the commonest but all of these cleared spontaneously. There was one case in which 30% saline was used as the intraocular irrigating fluid, causing retinal necrosis.

*Postoperative complications.* Seventeen postoperative complications occurred in 16 patients (Table X), giving a complication rate of 4·6%. Of the five children who developed a retinal detachment all had particularly unusual features. In one there had been a previous retinal detachment in the other (phakic) eye. Another child had ichthyosis and had had postoperative endophthalmitis in the other eye. A third child had chronic uveitis, a fourth had Lowe's syndrome, and a fifth was severely mentally retarded and institutionalised. In the last case the detachment was detected three years after surgery, and trauma from head banging was suspected.

Both cases of endophthalmitis were apparent on the first postoperative day. The infecting organisms were *Staphylococcus aureus* and *Staph. epidermidis*. Both the corneal complications occurred in contact lens wearers. The case of persistent inflammation was in a child with rubella cataract.

Strabismus is not mentioned in Table X. While it was universal in the congenital cases and a little less frequent in later onset cases, the squint was often present preoperatively and therefore could not be considered a postoperative complication. Some degree of posterior capsular opacification was present postoperatively in almost all the cases which had lens aspirations, but not all were of a degree to require capsulotomy.

TABLE X *Postoperative complications*

| | *Eyes* |
|---|---|
| Retinal detachment | 5 |
| Chronic aphakic glaucoma | 4 |
| Acute glaucoma | 2 |
| Endophthalmitis | 2 |
| Cystoid macula oedema | 1 |
| Corneal abscess | 1 |
| Corneal ulcer | 1 |
| Persistent inflammation | 1 |

TABLE XI *Secondary procedures – aspiration group*

| | *Eyes* |
|---|---|
| Posterior capsulotomy | 37 |
| Ant. seg. revision | 10 |
| Examination under anaesthetic | 7 |
| Squint surgery | 5 |
| Removal of sutures | 4 |
| Resuture of wound | 2 |
| Retinal detachment | 1 |
| Peripheral iridectomy | 1 |
| Cyclocryotherapy | 1 |

TABLE XIII *Visual results versus age at surgery in bilateral congenital cataracts*

| *Age at surgery (months)* | *1–2* | *3–4* | *5–6* | *7–12* |
|---|---|---|---|---|
| Mean vision | 0·32 (6/18) | 0·18 (6/33) | 0·23 (6/26) | 0·25 (6/24) |
| Vision >6/24 | 5 | 2 | 4 | 3 |
| Number | 6 | 7 | 7 | 6 |
| Mean follow-up (months) | 48 | 67 | 63 | 57 |

TABLE XII *Secondary procedures – lensectomy group*

| | *Eyes* |
|---|---|
| Examination under anaesthetic | 30 |
| Ant. seg. revision | 14 |
| Squint surgery | 8 |
| Capsulotomy | 5 |
| Removal of sutures | 5 |
| Division of synechiae | 2 |
| Release of incarcerated iris | 1 |
| Cyclocryotherapy | 1 |

TABLE XIV *Visual results – infantile cataracts*

| | |
|---|---|
| Mean visual acuity | 0·45 (6/13) |
| Mean age at surgery | 22·6 months |
| Mean follow-up | 56·9 months |
| Number | 10 children |

*Secondary procedures.* Overall, 128 subsequent procedures were performed on 82 eyes of 72 patients. Forty one of 109 (38%) eyes which had an aspiration had secondary procedures, the most common being a posterior capsulotomy (Table XI). In the lensectomy group 37 of 237 eyes (16%) had secondary procedures, with examination under anaesthetic being the commonest type (Table XII). This was usually performed to exclude glaucoma or infection.

The cases requiring anterior segment revision include those in which a vitreous strand was identified in the wound, posterior synechiae had formed, lens remnants were left, or the anterior chamber became shallow.

### *Visual results*

*Bilateral congenital cataract.* Table XIII shows the visual results in the better eye in cases of simple bilateral congenital cataract according to the age at surgery. Aphakia was corrected with contact lenses within one or two weeks of surgery, and only a minority (15%) discontinued lens wear. The average visual acuity was better when surgery was performed within the first two months of life, though the difference was not statistically significant ($\chi^2$ test, $p=0{\cdot}23$). In most cases strabismus was present, and the strabismic eye had a more marked degree of amblyopia.

*Unilateral congenital cataract.* These infants were optically corrected with a contact lens, and sound eye occlusion was begun immediately after surgery. The occlusion was of the order of 90% of the waking hours for the first few weeks and then gradually reduced, but in most cases the occlusion later become unreliable and rather haphazard.

Only six children were old enough to read the Snellen chart. Of these one child achieved 6/24 vision. This child was remarkable in that it was operated on at 7 weeks and the parents were compliant with the occlusion therapy. The other five were all poorly compliant of occlusion despite encouragement and explanation from medical, optometrical, and orthoptic staff, and all had corrected vision of 2/60 or worse. We consider that in the discussion with the parents of prospective surgery for unilateral congenital cataract mention should be made of the high non-compliance rate with the occlusion regimen.

*Infantile cataract.* Table XIV shows that these children achieved good visual results in the better eye. All these infants had apparently good

TABLE XV *Visual results – juvenile cataracts*

| | |
|---|---|
| Mean visual acuity | 0·68 (6/9) |
| Mean age at surgery | 82 months |
| Mean follow-up | 32 months |
| Number | 21 children |

TABLE XVI *Visual results – trauma*

| | |
|---|---|
| Mean visual acuity | 0·37 (6/16) |
| Mean age at surgery | 82 months |
| Mean follow-up | 21·5 months |
| Number | 9 children |

fixation prior to the development or progression of the cataracts. They were all bilateral.

*Juvenile cataract.* The children whose cataracts developed after the age of 2 years achieved good visual results. All but three of these cases were bilateral, and the acuities shown are in the better eye (Table XV).

*Traumatic cataract.* All the trauma cases were unilateral, so that in some amblyopia was a problem. The visual results are given in Table XVI.

## Discussion

Just over half the children in this study had simple cataracts. In 44% the cataract was associated with a congenital syndrome or ocular anomaly or was a secondary cataract. The heterogeneity of the diagnoses reflects the referral pattern of the Hospital for Sick Children, which functions as a tertiary referral centre. About a third of simple cases in our study were familial. This compares with more than 55% in another London study[1] and underlines the point that most inherited cases are simple; our figures are biased by the large proportion of complicated cases. The high incidence of retrolental abnormalities is also reflected in vitreous haemorrhage being the commonest operative complication.

It is regrettable that the mean ages of presentation in bilateral congenital cataracts with and without a family history are similar (4·1 and 4·6 months). Infants born into families with a history of cataracts should be prime candidates for early detection and surgery if necessary. Reminders and encouragement for an early check should be given by the ophthalmologist and paediatrician at every opportunity.

While congenital rubella was not uncommon in the early years of the study, in recent years most cases with this syndrome have been referred from abroad. With the availability of the measles-mumps-rubella vaccine in the UK cataracts due to rubella embryopathy are now entirely preventable. If rubella is considered as a possible aetiology, rubella antibodies should be measured on maternal and infant serum. The lens material removed at surgery should be cultured to grow the virus. The virus may be grown from children up to 4 years of age. In cases of congenital rubella we use steroid drops prior to surgery, subconjunctival steroids at operation, and frequent steroid drops after surgery.

Only one case of cataract due to galactosaemia was operated on. This is because, even though galactosaemia is high on every list of causes of congenital cataracts, the cataracts usually disappear within days of beginning a lactose-free diet.

No cases of corneal endothelial decompensation were noted. At present all children undergoing lens surgery at The Hospital for Sick Children have photographs taken of the corneal endothelium at each subsequent procedure. The results of this study will be published in due course.

For the children in this study those with dislocated lenses and infantile and juvenile cataracts had very good visual outcomes. In the past, surgery for dislocated lenses had a high risk of complication and was not to be undertaken lightly.[2,3] Modern surgical techniques have changed the indications for operating on a child with a dislocated lens.[4] We believe that a child should have the lens removed and wear aphakic correction as soon as the level of vision is inadequate for normal life or the situation of the lens is such as to make amblyopia likely.

Children with simple bilateral congenital cataracts removed and optically corrected at an early age can expect reasonable vision. If 6/24 vision is taken as a level above which a child should be able to be educated at a normal school with minimal extra help, five of six children in this early surgery group achieved better than this level of vision. Earlier surgery and correction are probably associated with better visual results, though our numbers were small and the results were not statistically significant. By the time the visual defect is obvious to the parents, the optimum time for surgery is likely to have passed. Consequently, to detect the cases early enough a test for obstruction of the red reflex on ophthalmoscopy must be part of the checking of every newborn and 6-week baby.[5-7] Ophthalmologists should encourage and instruct their paediatric and general practice colleagues to include this.

In children with unilateral congenital cataracts the visual results are disappointing and are not comparable with those reported by some other authors.[8,9] Opaque contact lenses[10] have been tried without success in our department, and we rely on a rigorous occlusion programme. Nevertheless dense amblyopia remained the norm. The cost effectiveness of surgery in these unilateral cases remains controversial, especially since a good visual result may lead to diplopia.[11]

Because of the advent of the horizontally mounted, vertically aimed YAG laser, we intend in future to perform a lens aspiration followed by laser capsulotomy, in all cases with the exceptions of ectopia lentis, cases in which an aspiration on the other eye was difficult or complicated, posterior lenticonus, and PHPV and other retrolental abnormalities. In these cases lensectomy will continue to be the preferred procedure. The main advantage of an aspiration is that implantation of a posterior chamber intraocular lens remains an option which can be considered in the future. There are also the theoretical advantages of a lesser risk of retinal detachment and cystoid macular oedema. One infant in the study with a limited life expectancy, and considerable systemic problems related to the cerebro-oculo-facial-skeletal syndrome, had an intraocular lens implanted at the primary operation. However, because of the rapidly changing refraction in infancy, the unknown long term effects of intraocular lens implantation, and the high acceptance rate of contact lens use, we do not recommend intraocular lens implantation at present.

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# Quantification of lens opacification with a commercially available lensometer

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## Abstract

**A clinical trial was undertaken to determine whether a commercially available lens opacity meter (LM701), which measures backward scattered light from the lens, provides reliable clinical information about the effect of lens opacities on visual acuity. At the 0·001 level of probability we found a significant relationship between the lens opacity meter reading and both the Snellen acuity and patient's age. For a given individual there was also a relationship between the difference in the lens opacity readings between eyes and the difference in the Snellen acuities. We could not demonstrate a relation between the lens opacity reading and either the refractive error, pupil size, or near visual acuity at this level of significance.**

There is an increase in both the absorption and the scattering of light by the human lens during aging. For a given light exposure age related changes in the lens will cause a variation in both the total irradiance and the spectral distribution of the irradiance of the retina. Transmission losses are particularly significant at wavelengths shorter than 450 nm.[1] These changes are not solely the result of an increased thickness of the lens or a reduction in pupil diameter,[2] but are in part due to aggregation and postsynthetic changes in the lens proteins, which produce local differences in the index of refraction. These changes produce scattering of light which is manifest subjectively as increased glare and objectively as reduced visual acuity.

Deciding on the contribution of lens opacities toward visual acuity loss can be a clinical challenge, such that a technique to quantify lens opacity would be of value in the assessment of patients with cataract. Some of the clinical effects of lens opacity may be gauged from an assessment of the visual acuity, while a simple and objective assessment of lens opacity can be gained by retroillumination or by slit-lamp examination. A number of techniques have been developed in an attempt to quantify lens opacity.[3] These include photography of the lens by retroillumination[4] and densitometric pattern analysis of the photographic negative[5-7]; resolution test target projection ophthalmoscopy[8]; the measurement of light back scattering from defined regions of the lens[9,10]; microdensitometry of photographic negatives of the lens obtained by using the Scheimpflug principle[11,12]; the measurement of lens fluorescence spectra[13]; the grading of opacity by comparison with standards at slit-lamp examination[3,14]; the comparison of retinal sensitivity loss at different wavelengths[15]; and the measurement of the contrast transfer ratio.[16] None of these methods have been adapted to provide a source of quick and reliable information for the clinician.

Recently a commercially available device termed a lensometer has become available. This instrument, the lens opacity meter 701 (Interzeag Gmbh., Switzerland), utilises a beam of light 1·5 mm in diameter at 700 nm to produce back scatter from opacities on the optic axis of the lens. The back scattered light from the lens is then detected at a fixed angle of 27° with respect to the incident beam, converted into an electric impulse, and recorded on an arbitrary scale between 0 and 100.[17,18] A previous investigation using this instrument on a population with normal visual acuity reported an increase in lens opacity values with age, with a range from 4 to 25 units.[18,19] Data from 13 patients with a variety of types of lens opacities showed that detection was best for diffuse opacity of the lens and that higher values were obtained following mydriasis.[18]

To determine if this instrument has a role in the clinical assessment of patients with lens opacities we present the results of 102 patients in whom cataract was suspected as the sole cause of a reduction in visual acuity, and in whom we correlated the refraction and visual acuity with the lensometer reading.

## Materials and methods

Patients were selected from a population attending the refraction clinic at Moorfields Eye Hospital. For each patient a record was made of their subjective refraction, and their best corrected vision was measured with a standard Snellen chart under normal clinical conditions, which was then expressed as their decimal acuity. The design and handling of the LM701 is similar to that of a photographic slit-lamp, with the patient's chin placed on a rest and the instrument aligned and operated with a joy stick. A more complete description of the instrumentation is contained elsewhere.[17,18] Observations were made in reduced illumination without dilatation of the pupil. For each eye the pupil diameter was recorded, and five consecutive readings were made with the patient fixating the instrument target, or with the instrument aligned with the centre of the pupil when this was prevented by poor acuity. The five readings were processed by an inbuilt minicomputer and the mean and the standard deviation derived. Left and right eyes were analysed separately except for difference analysis. The criterion that was adopted for statistical significance was $p=0{\cdot}001$.

Patients with a visual acuity of less than 6/6 had a full ophthalmic examination, including funduscopy with dilatation, and the identification of a posterior segment abnormality that could account for their loss of visual acuity was the only

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criterion for exclusion from the study. Eyes in which a posterior chamber intraocular lens had been implanted with an intact posterior lens capsule were included, but four aphakic eyes were excluded from the statistical analysis.

The data were assessed by both linear and nonlinear regression analysis, and, although a slightly better fit was obtained with the latter, for the sake of clarity only linear regression is shown.

## Results

Two hundred and two eyes of 102 patients (44 males and 58 females, age range 19 to 92 years, mean 65·9 years, SD=16·2) were examined for this study. Two patients were uniocular. There were 57 patients (60 eyes) who had had an intraocular lens implant, and 11 eyes in which analysis was not possible because of incomplete data. 86% of the patients were over the age of 50 years. The mean patient age for the right eyes was 63·6 years (62 patients, SD=16·25 years), and the mean pupil diameter was 4·16 mm (SD=1·22mm). The mean patient age for the left eyes was 62·1 years (58 patients, SD=17·42 years), and the mean pupil diameter 4·17 mm (SD=1·27 mm). A two tailed $t$ test comparing these groups was not significant (age, p=0·603; pupil diameter, p=0·9).

As expected, there was a significant reduction in the pupil diameter of the unoperated eyes with increasing age; the regression for right eyes had a slope of −0·0434 and an intercept of 6·923 (r=−0·5795, df=60, p<0·0001), while the left eyes had a slope of −0·0484 and an intercept of 7·175 (r=−0·6619, df=56, p<0·0001). Despite obtaining readings in reduced illumination, 43 of 127 (33·8%) of pupil diameters were less than 4 mm; however, the diameters of all pupils were greater than the diameter of the LM701 beam.

Although values for lens opacity of up to 100 were possible, no patient in this study had a value greater than 56, despite an acuity of less than 6/60 in some patients. For phakic eyes 71 of 125 (56·8%) of the lensometer readings were greater than 20, and there was a rapid increase in readings over the age of 60 years. The results of linear regression analysis of all of the data are shown in Table 1, and it may be seen that there is a highly significant relationship between the lensometer readings and age, visual acuity, and visual acuity difference between pairs of phakic eyes. The changes in lensometer readings as a function of age for phakic patients are illustrated in Figure 1.

TABLE 1 *Results of linear regression analysis*

| *LOM reading versus:* | | *Slope* | *Intercept* | *r* | *df* | *p* |
|---|---|---|---|---|---|---|
| Age | R | 0·3866 | −0·4820 | 0·6234 | 62 | 0·0000 |
| | L | 0·3442 | 0·6931 | 0·5722 | 61 | 0·0000 |
| Pupil size | R | −1·5584 | 29·114 | −0·1747 | 64 | 0·1607 |
| | L | −2·1880 | 31·472 | −0·2613 | 61 | 0·0386 |
| Visual acuity | R | −15·953 | 34·041 | −0·5816 | 65 | 0·0000 |
| | L | −12·708 | 30·934 | −0·5179 | 63 | 0·0000 |
| Visual acuity (IOL) | R | 1·230 | 10·010 | 0·0395 | 30 | 0·8300 |
| | L | 0·626 | 9·395 | 0·0497 | 28 | 0·7943 |
| Near acuity | R | −14·814 | 35·277 | −0·3718 | 64 | 0·0021 |
| | L | −11·303 | 31·801 | −0·3326 | 61 | 0·0077 |
| Spherical equivalent | R | −0·8534 | 21·467 | −0·3674 | 60 | 0·0033 |
| | L | −0·5468 | 20·83 | −0·2139 | 59 | 0·0979 |
| Cylindrical error | R | −0·0141 | −0·661 | −0·1564 | 60 | 0·2246 |
| | L | −0·0284 | −0·337 | −0·3198 | 59 | 0·0120 |
| Acuity (phakic) | | −13·732 | 1·0513 | −0·6464 | 32 | 0·0000 |
| difference (IOL) | | −21·010 | 1·1080 | −0·4586 | 38 | 0·0029 |

LOM=lensometer. IOL=intraocular lens.

Figure 2 shows a plot of the lensometer reading versus the distance visual acuity for phakic eyes plotted as the decimal acuity. In both the right and left eyes there was a significant increase in the lensometer reading with a decrease in the visual acuity. Pseudophakic eyes were separately analysed and there was no significant correlation between the lensometer reading and the visual acuity (Table 1).

In a comparison between the lensometer reading and refractive error for phakic eyes, 64 of 119 eyes included (53·8%) were myopic. There was no significant relationship between the refractive error of these eyes and lensometer reading at the p=0·001 level (Table 1). Similarly, there was no relationship between lensometer reading and refractive error when either sphere or cylinder were analysed separately.

To permit a comparison between the two eyes of each patient, we compared the difference between the lensometer readings for the right and left eyes with the difference between the visual acuities. The result again indicated that a reduction in visual acuity correlated with an increase in the lensometer reading at the level of significance of p<0·0001. When eyes containing intraocular lenses were similarly analysed, the significance was less marked (p>0·001) (Table 1). The relationship between the near visual acuity and the lensometer reading approached but did not attain significance at the p=0·001 level.

## Discussion

The development of cataract is associated with a loss of visual acuity that is a function of both the increased absorption and scatter of light by the lens. Using the lens opacity meter LM701 we found a statistically significant correlation between the LOM reading and both age and visual acuity in phakic eyes. There was also a significant correlation between the difference in the LOM reading and the difference in visual acuity between eyes. In contrast, there was no correlation between the LOM reading and the near visual acuity or refraction, or with pupil size despite a reduction of pupil size with increasing age.

An age related increase in the scatter of light by the lens has been previously noted.[10] [19] Using light back scatter from defined regions of the lens, Ben-Sira *et al*[10] noted a continuous increase in opacity values for the anterior cortex from the age of 20 years in patients with visual acuity maintained at 6/6, whereas opacity values for the nucleus did not begin to increase until after 50 years of age. In contrast, using microdensitometric analysis of Scheimpflug photographs, Hockwin *et al*[12] recorded a continuous increase in the light scattered from the nucleus throughout life. An increase in the fluorescence from the

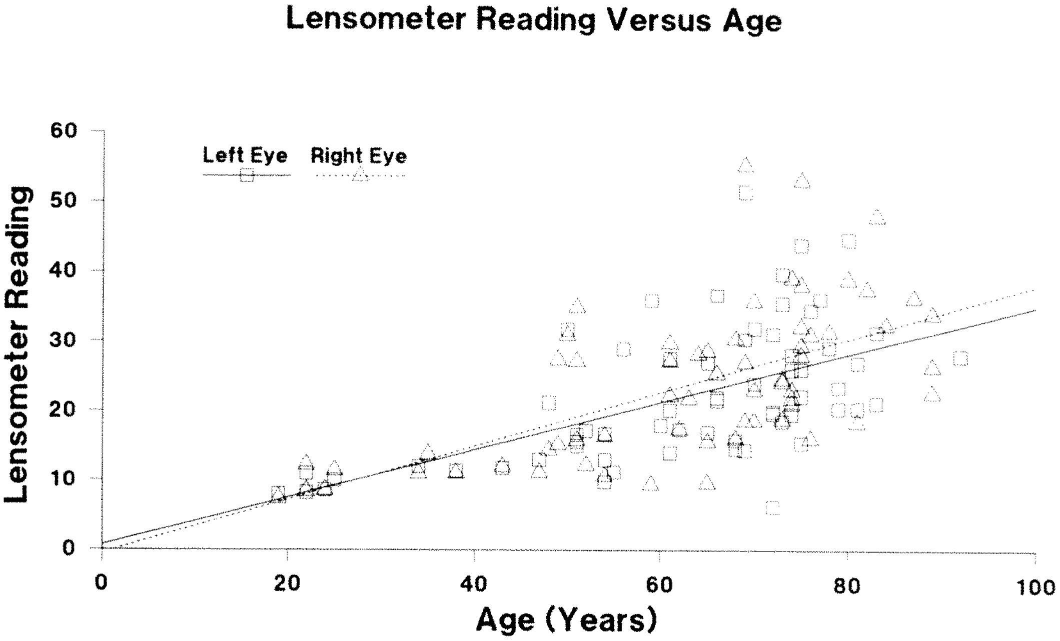

*Figure 1: A scatter plot of the lensometer reading (instrument units) versus age in years for phakic patients. The regression lines for the right and left eyes and drawn separately. Note that there is a rapid increase in the higher lensometer values with age, and that the origin is very close to a zero lensometer reading.*

deeper layers of the cortex has also been observed after the age of 30 years.[1] From these data it follows that the eye can tolerate an increased colouration of the lens with some loss of overall and spectral transmission, and an increase in back scatter, without loss of visual acuity.

A number of different techniques have been used to calibrate the light that is back scattered from the lens. For example Goldmann[9] and Ben-Sira *et al*[10] used part of the illuminating beam from a standard slit-lamp as a reference source, while Wolf and Gardiner[20] used a stabilised light source to provide a photometric assay. Using the instrument under study De Natale *et al*[19] found that there was a relationship between age and opacity up to the age of 65 years. This correlates with the continuous increase of nuclear opacity with age demonstrated by a Scheimpflug camera.[12] We confirmed an increase in the LOM reading with age. However, unlike the study by De Natale *et al*[19] we have included patients with pathological lens opacities in addition to those with aging changes. This is reflected in the higher values for LOM readings of up to 56 instrument units in our study as opposed to 30 in their patients.

It may be assumed that there is a relation between the light that is back scattered from the lens and that which is forward scattered to the retina, but the form of this relation is not known and may depend on the nature and distribution of the light scattering elements in the lens. However, there is not a clear relationship between light scattered by the lens and disability as measured by visual acuity.[21] Although some taxonomic studies emphasise the morphological features of lens opacity,[14] we have not attempted to correlate the LOM reading with the type of lens opacity. It should be noted that Wegener and Hockwin[18] studied 13 cataractous patients with a LM701 and noted an increase in the LOM value of approximately 4 units following mydriasis; they also considered that the instrument provided better evaluation of homogeneous rather than localised lens opacities.

In conclusion, we found the instrument to be

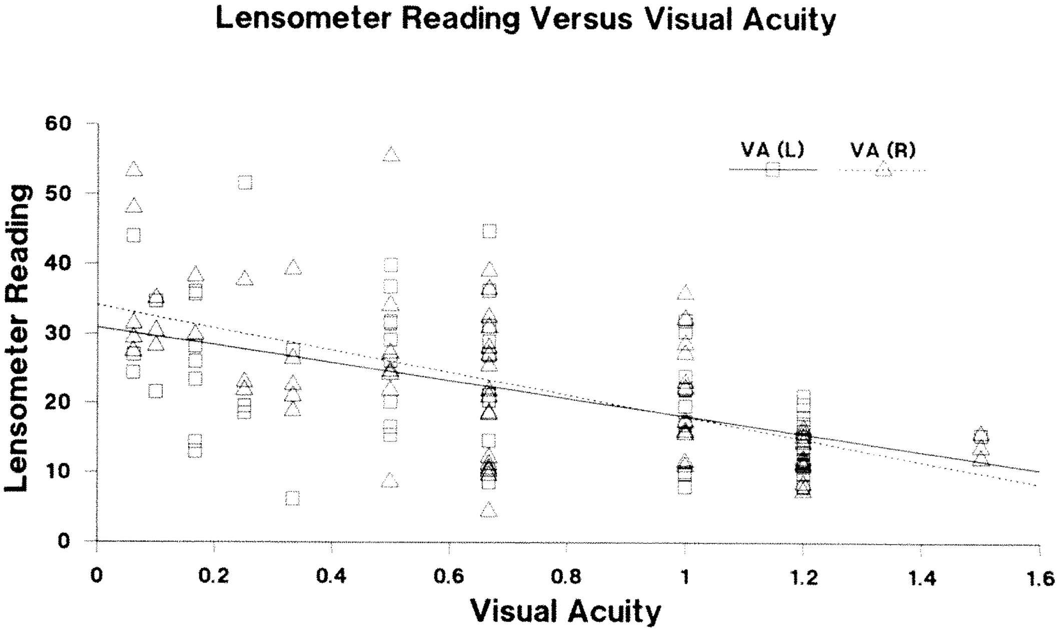

*Figure 2: A scatter plot of the lensometer reading as a function of the decimal visual acuity. Although in the population there is a wide spread of lensometer readings at each visual acuity level, the regression indicates that there is a significant negative correlation, such that an increased lensometer value corresponds to a reduced visual acuity.*

of little help in the estimation of the contribution made by lens opacity to visual loss on an individual basis, but after linear regression the LOM meter provided useful information on the contribution of lens opacities to visual acuity loss in a population with cataract. An instrument of this design may thus be of value in population studies to record the natural history of lens opacity, the ocular side effects of drug therapy, and the therapeutic effect of anticataract drugs.[3] There was a wide variation in the value for lens scatter within a given age group and a wide spread of LOM values for the other variables examined. This variability may be the result of loss of retinal sensitivity and optic nerve function with aging, absorption by the lens, or morphological differences between lens opacities.

The authors have no proprietary interest in the LM701 lensometer.

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# Factors relating to visual acuity in children who have been treated for convergent squint

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## Abstract

**Retrospective analysis of a selected sample of children who presented with convergent squint has shown that abnormal meridional hypermetropia (3·5 D or more) at age 1 was the principal factor associated with severe amblyopia (6/24 or less) remaining after conventional treatment. Neither the reported age of onset nor delay in presentation influenced the final visual outcome.**

It is widely believed that early onset of squint and/or delay in starting treatment have an adverse influence on amblyopia. Evidence for this is presented in Tables 3, 4, and 5 of Worth's book.[1] They present the final visual results 'with optical correction and after all possible means have been used to remove any acquired amblyopia'. The only attempt to confirm this appears to be that of Costenbader *et al*.[2] Like Worth they recognised that records of the age of onset of squint may be unreliable, but their conclusion was different: 'while the average age of onset may not be significant, the average duration of the squint before treatment is most significant in the production of amblyopia'.

This difference of opinion should be resolved, particularly as infantile ametropia[3] has recently been identified as another factor possibly relevant to the incidence and severity of amblyopia. The present study assesses the association between these three factors and the severity of amblyopia in a group of treated children. They were selected on the basis that they were living in a particular area at age 1 year and refracted at that age. In carrying out the study we recognised that there were certain unavoidable difficulties, namely, that the reported age of onset may be inaccurate, and sometimes not available; and compliance with treatment was difficult to assess.

TABLE I *Age of onset*

| *Hypermetropia at 1 year* | | *Age of onset in months* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | *0–11* | *12–23* | *24–35* | *36–47* | *48–59* | *60+* | *?* |
| 3·5+ | 6/18 or better | 2 | 2 | 3 | 5 | 1 | 4 | 5 |
| | 6/24 or worse | 1 | 2 | 1 | 2 | – | – | 6 |
| <3·5 | 6/18 or better | 4 | 8 | 8 | 5 | 5 | 5 | 17 |
| | 6/24 or worse | 2 | – | – | 2 | – | – | – |

## Patients and methods

One hundred and sixty one children (approximately 4·3% of the population) born between January 1974 and December 1978 and who were resident in and around the town of Kettering at age 1 year have presented to us with convergent squint. This report concerns 90 of these, who were refracted at 1 year, and did not have any of the following conditions: uniocular congenital cataract, colobomata, congenital nystagmus, or Down's syndrome.

TABLE II *Duration of squint*

| *Hypermetropia at 1 year* | | *Duration of squint in months before treatment* | | | | |
|---|---|---|---|---|---|---|
| | | *0–2* | *3–4* | *5–6* | *7+* | *?* |
| 3·5+ | 6/18 or better | 8 | 6 | 1 | 2 | 5 |
| | 6/24 or worse | 3 | 2 | – | 1 | 6 |
| <3·5 | 6/18 or better | 16 | 11 | 4 | 4 | 17 |
| | 6/24 or worse | 1 | – | 1 | 2 | – |

Those children born between 1974 and 1977 were refracted after cycloplegia with atropine 1% at age 1 year,[4] and those born in 1978 were refracted after cycloplegia with cyclopentolate 1% at age 1 year. To increase the number of children available for statistical analysis these two groups have been combined. Allowance has been made for the observation[5] that retinoscopy after atropine cycloplegia shows approximately 0·5 D more hypermetropia than after cycloplegia with cyclopentolate 1%. In the following tables the figure for the cyclopentolate equivalent is quoted. 3·5 or more D or hypermetropia in the most hypermetropic meridian of each pair of eyes (meridional hypermetropia) has been recorded as abnormal hypermetropia. All the 90 children were treated conventionally with spectacles, occlusion, and operation when necessary.

Thirty six of them had been entered into a randomised trial of treatment from age 1 year, of whom 16 were drawn for treatment. All 36 have been included because treatment from 1 year did not obviously alter the visual outcome.[6]

Visual acuity was measured with the linear Sheridan-Gardiner or Snellen tests, and it is the last known acuity for the worse eye which is reported.

## Results

The last known acuities are recorded in two tables. In Table I the ages of onset are shown and in Table II the duration of squint before presentation. In each table, the children are divided into two groups: those who had 3·5 or more D meridional hypermetropia at age 1 year and those who had less than 3·5 D meridional hypermetropia at 1 year.

The findings recorded in each table were subjected to three-way contingency analysis. No evidence was found to suggest that the age of onset or duration of the squint between onset and presentation significantly determined the visual outcome. The only significant predictor of a poor

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TABLE III *Meridional hypermetropia and final acuity*

| | *Last known visual acuity* | |
|---|---|---|
| *Meridional hypermetropia at age 1 year* | *6/18 or better* | *6/24 or less* |
| 3·5 D or more | 22 | 12 |
| <3·5 D | 52 | 4 |

$\chi^2=9{\cdot}625$, $p<0{\cdot}01$.

final acuity of 6/24 or less was meridional hypermetropia (Table III).

## Discussion

Worth[1] believed that early onset of squint or delay in starting treatment was associated with lower acuity retained by the squinting eye after treatment. Costenbader *et al*[2] reported observations on 316 children, but their conclusions referred only to the incidence of amblyopia (20/40 or less) associated with squint. We were interested in the severity of amblyopia. In these 90 children severe amblyopia (6/24 or less) remaining after treatment was not related to the reported age of onset of the squint, nor to any delay in starting treatment. Three possible factors could contribute to the difference between our findings and those of Worth.[1] Firstly, 50% of his children had 6/36 visual acuity or less after treatment, whereas only 15% of ours fared as badly. Secondly, since 1981 we have watched many children in whom we expected squint to appear, but nevertheless we still found it quite difficult to date the exact time of onset of the squint. The recorded age of onset of squint for many of the children in this sample, particularly those who were abnormally hypermetropic in infancy, may not, therefore, be strictly accurate. Thirdly, if we had studied larger numbers of children, it is possible that significant associations between the age of onset or duration of squint and relatively severe amblyopia might have emerged.

However, our principal conclusion is that in this limited number of children abnormal hypermetropia at the age of 1 year was the principal factor associated with severe residual amblyopia even after full treatment. The age of onset of squint and delay in starting treatment do not appear to be of as much importance as was previously thought.

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# A prevalence survey of ophthalmic diseases among the Turkana tribe in north-west Kenya

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## Abstract

**A prevalence survey of ophthalmic disease was conducted among the Turkana tribe in north-west Kenya. Altogether 900 people were examined in different sites of the semiarid and arid Turkana region. The findings show the prevalence of blindness to be 1·1% and the prevalence of blindness in one eye to be 6·8%. The major causes of blindness up to age 35 were corneal disease from xerophthalmia and trachoma and above age 45 cataract. Trauma was a major cause of monocular blindness. The prevalence of trachoma and its complications was 42·8% and the prevalence of cataract 5·2%. Cataract begins to form at an early age (25–35). The prevalence of xerophthalmia was 44%. These findings are similar to previously reported studies in Africa, especially in semiarid areas. The main remedy lies in improvement of education and the environment.**

The prevalence of blindness in Africa by the World Health Organisation's definition of blindness, which is a visual acuity of less than 3/60 in the better eye, is between 1·2% and 1·5%,[1,2] or 4·8–6 million people. A further 6 million are severely handicapped. According to estimates, in the year 2000 the number of blind people in Africa will be 12 million. The major causes of blindness in Africa are senile cataract, ocular infections (especially trachoma and onchocerciasis), and malnutrition. The causes of blindness vary from region to region.

A series of ocular surveys were performed throughout rural Kenya between 1976 and 1983.[3] The prevalence of blindness in the whole of Kenya was found to be 0·7% by the WHO definition. The prevalence of significant visual loss (visual acuity less than 6/18 in the better eye) was 2·5%. The major causes of blindness were found to be senile cataract (38% of total blindness), trachoma (19%), glaucoma (9%), senile macular degeneration (7%), and refractive errors (6%); all other causes constituted 22%. Onchocerciasis (river blindness), an important cause of blindness in a small area of Western Kenya several decades ago, was eliminated in the 1950s.

A prevalence survey of ophthalmic diseases was conducted among the Turkana tribe in north-west Kenya. This tribe, which belongs to the Nilo Hamite group of tribes,[4] numbers about 200 000 people (an estimate of health workers in Lodwar, the regional centre), 80% of them nomads and 20% settlers. This is the first survey of ocular problems done in the area, which is desert or semidesert. The aims of the study were to ascertain the prevalence of certain diseases in the tribe and to determine their prevalence among different age and population groups.

## Materials and methods

Nine hundred people were examined at 10 different sites in the Turkana region among the nomads at 5 sites, the settlers at 3 sites, fishermen at 1 site, and settlers living in relief camps at 1 site. The sites were chosen after consulting the team of the Community Based Health Care in Lodwar, Turkana District. The choice was made in such a way that the sample from each group (nomads, settlers, etc) was proportional to the population size of the group and in different areas in Turkana. In each site the people examined were selected randomly by examining the entire population of one of the locations. We examined 406 males (45·1% of the total population) and 489 females (54·3% of the total population). (The sex of five people was not listed in their forms.) Eye examinations included visual acuity tests with E and C charts and an external eye examination by sunlight, a torch, and a magnifying glass.

Eyes were examined for the following features and diagnoses:

(a) *Visual acuity.* Blindness was defined as a visual acuity of less than 3/60 in the better eye with best correction. Monocular blindness was defined as visual acuity of less than 3/60 in the worse eye with best correction in that eye.

(b) *Trachoma.* Each of the following signs was sufficient for the diagnosis of trachoma: follicles on the upper tarsal conjunctiva, follicles on the limbus or their sequelae – namely Herbert's pits, a typical conjunctival scarring, or a prominent vascular pannus especially in the upper limbus.

The staging of trachoma was a modification of the Wilson classification[5]: (1) Active trachoma: at least five follicles seen clearly on the upper tarsal conjunctiva and/or a scar and sufficient thickening of the conjunctiva so that the deep blood vessels are not seen. (2) Inactive trachoma: scarring seen clearly in the upper tarsal conjunctiva. (3) Inactive trachoma with beginning of complications: trichiasis – at least one eyelash rubs the eyeball or there is evidence of epilation. (4) Further complications: opacity at the centre of the cornea thick enough to obscure part of the pupil.

(c) *Cataract.* Opacity of the lens and inability to see the fundus clearly were criteria for the diagnosis of cataract. The possible etiology (traumatic/non-traumatic) was determined from the history.

(d) *Xerophthalmia and keratomalacia.* The following symptoms and signs were sufficient for the diagnosis of xerophthalmia: a history of nightblindness and/or Bitot spots.

In cases where diagnosis was uncertain, the

TABLE I *Visual acuity in the better eye*

| | *No of patients* | *6/6–6/18* | *6/21–6/60* | *5/60–3/60* | *3/60–1/60* | *Less than 1/60* | *NLP* | *Unmeasurable* |
|---|---|---|---|---|---|---|---|---|
| Males | 406 | 317 | 5 | 1 | 0 | 0 | 4 | 79 |
| Females | 489 | 382 | 7 | 1 | 1 | 4 | 1 | 93 |
| Total | 895 | 699 | 12 | 2 | 1 | 4 | 5 | 172 |

NLP=no light perception.

patients were referred for further examination to the regional hospital in Lodwar.

## Results

The main findings were as follows.

### BLINDNESS

Visual acuity in the better eye (with best correction) is shown in Table I. Causes of blindness are shown in Table II.

The prevalence of blindness was 1·1% (10 cases). Under age 25 the prevalence was 0·2% (1 case), at ages 25–54 it was 1·4% (5 cases), and at 55 and over it was 12·5% (4 cases). 1·3% of the females examined were blind (6 cases) and 1·0% of the males (4 cases). Four cases could be attributed to senile cataract, 2 to complications of trachoma, 3 to complications of xerophthalmia, and 1 case (male aged 40) could not be attributed to any of the above diagnoses.

TABLE II *Major causes for blindness*

| | *Senile cataract* | *Trachoma complications* | *Xerophthalmia complications* | *Unknown causes* |
|---|---|---|---|---|
| Females | 4 | – | 2 | – |
| Males | – | 2 | 1 | 1 |
| Total | 4 | 2 | 3 | 1 |

### MONOCULAR BLINDNESS

Visual acuity in the worse eye (with best correction in that eye) is shown in Table III. The causes of monocular blindness are shown in Table IV.

The prevalence of monocular blindness was 6·7% (61 cases). Nine eyes reached a state of phthisis (1·0%). Under age 25 the prevalence as 2·0% (10 cases). At ages 25–54 it was 10·3% (37 cases), and at 55 and over it was 43·8% (14 cases). 7·6% of the females had monocular blindness (37 cases) and 5·9% of the males (24 cases). Eight cases could be attributed to senile cataract, 9 to complications of trachoma, 13 to trauma, and 24 could not be attributed to any of the above (of these cases 14 had a corneal opacity – 9 males and 5 females, 1 male had a lens opacity, and 5 had both corneal and lens opacities. Three suffered from phthisis (females), and 1 male aged 40 had no corneal or lens lesion.

TABLE III *Visual acuity in the worse eye*

| | *No of patients* | *6/6–6/18* | *6/21–6/60* | *5/60–3/60* | *3/60–1/60* | *Less than 1/60* | *NLP* | *Unmeasurable* |
|---|---|---|---|---|---|---|---|---|
| Males | 406 | 297 | 6 | 0 | 1 | 5 | 18 | 79 |
| Females | 489 | 347 | 12 | 0 | 4 | 9 | 24 | 93 |
| Total | 895 | 644 | 18 | 0 | 5 | 14 | 42 | 172 |

TABLE IV *Major causes of blindness in one eye*

| | *Senile cataract* | *Trachoma complications* | *Xerophthalmia complications* | *Trauma* | *Unknown causes* |
|---|---|---|---|---|---|
| Females | 6 | 6 | 5 | 10 | 10 |
| Males | 2 | 3 | 2 | 3 | 14 |
| Total | 8 | 9 | 7 | 13 | 24 |

TABLE V *Prevalence of trachoma in age groups*

| *Age groups* | *No. of patients* | *No. of trachoma patients* | *% of trachoma patients* |
|---|---|---|---|
| 0–4 | 150 | 50 | 33·3 |
| 5–9 | 97 | 35 | 36·1 |
| 10–14 | 126 | 36 | 28·6 |
| 15–24 | 137 | 53 | 38·7 |
| 25–34 | 237 | 122 | 51·5 |
| 35–44 | 79 | 47 | 59·5 |
| 45–54 | 42 | 26 | 61·9 |
| 55–64 | 22 | 11 | 50·0 |
| 65–74 | 7 | 4 | 57·1 |
| 75+ | 3 | 1 | 33·3 |

### TRACHOMA

The prevalence of trachoma in at least one eye as a function of age is shown in Table V.

Severity of trachoma as a function of age is depicted in Table VI. The prevalence in at least one eye was 42·8% (385 cases). The highest prevalence of active trachoma was in the under 5 age group: 28·7% (43 children out of 150 examined). Inactive trachoma began to appear at the 5–9 year age group – 18·6% (18 children out of 97 examined). At ages 35–44, 50% of the people examined already had conjunctival scarring due to trachoma (21 out of 42 people examined). No further rise in percentage of scarring was noted above this age group. Trichiasis and entropion began to appear in the 25–34 age group (1·7%, or 4 cases out of 237 examined). At the same age group corneal opacities began to appear (1·3%, or 3 cases).

### CATARACT

The prevalence of cataract in at least one eye as a function of age is shown in Table VII.

The prevalence of cataract in at least one eye was 5·2% (47 cases). There were 2 cases up to the age of 25 years (0·7%). At 25–34 years 3·0% suffered from cataract in at least one eye (7 cases out of 237 examined). There was a steady rise in cataract prevalence up to the 55–64 age group (54·5%). Of the 47 cataract cases 20 were in males (4·9% of all males examined) and 27 in females (5·5% of all females examined). Forty four cataract cases were non-traumatic, and 5 were due to trauma (2 of these suffered from non-traumatic cataract in the other eye). All trauma cases were females in the 45–64 age group.

### XEROPHTHALMIA

The prevalence of xerophthalmia as a function of age in at least one eye is shown in Table VIII. The prevalence was 4·4% (40 cases). The highest prevalence was at ages 15–24 (13·1%, 18 cases). Twenty three were males (5·7% of all males examined) and 17 females (3·5% of all females examined).

### PURULENT CONJUNCTIVITIS

The prevalence of purulent conjunctivitis was 1·9% (17 cases). The highest prevalence was at ages under 5 (6·0%, 9 cases), and 45–54 (7·1%, 3 cases).

TABLE VI *Severity of trachoma in age groups*

| *Age groups* | *No. of patients* | *(0)* | | *(1)* | | *(2)* | | *(3)* | | *(4)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | % | *No.* | % | *No.* | % | *No.* | % | *No.* | % | *No.* |
| 0–4 | 150 | 66·7 | 100 | 28·7 | 43 | 4·7 | 7 | 0 | 0 | 0 | 0 |
| 5–9 | 97 | 63·9 | 62 | 17·5 | 17 | 18·6 | 18 | 0 | 0 | 0 | 0 |
| 10–14 | 126 | 71·4 | 90 | 8·7 | 11 | 19·8 | 25 | 0 | 0 | 0 | 0 |
| 15–24 | 137 | 61·3 | 84 | 10·2 | 14 | 28·5 | 39 | 0 | 0 | 0 | 0 |
| 25–34 | 237 | 48·5 | 115 | 6·8 | 16 | 41·8 | 99 | 1·7 | 4 | 1·3 | 3 |
| 35–44 | 79 | 40·5 | 32 | 3·8 | 3 | 53·2 | 42 | 1·3 | 1 | 1·3 | 1 |
| 45–54 | 42 | 38·1 | 16 | 9·5 | 4 | 50·0 | 21 | 2·4 | 1 | 0 | 0 |
| 55–64 | 22 | 50·0 | 11 | 0 | 0 | 31·8 | 7 | 9·1 | 2 | 9·1 | 2 |
| 65–74 | 7 | 42·9 | 3 | 0 | 0 | 28·6 | 2 | 0 | 0 | 28·6 | 2 |
| 75+ | 3 | 66·7 | 2 | 0 | 0 | 33·3 | 1 | 0 | 0 | 0 | 0 |

TABLE VII *Prevalence of cataract in at least one eye*

| *Age groups* | *No. of patients* | *No. of cataract patients* | *% of cataract patients* |
|---|---|---|---|
| 0–4 | 150 | 0 | 0 |
| 5–9 | 97 | 0 | 0 |
| 10–14 | 126 | 1 | 0·8 |
| 15–24 | 137 | 1 | 0·7 |
| 25–34 | 237 | 7 | 3·0 |
| 35–44 | 79 | 7 | 8·9 |
| 45–54 | 42 | 13 | 31·0 |
| 55–64 | 22 | 12 | 54·5 |
| 65–74 | 7 | 3 | 42·9 |
| 75+ | 3 | 3 | 100·0 |

TABLE VIII *Prevalence of xerophthalmia in age groups*

| *Age groups* | *No. of patients* | *% of xerophthalmia patients* | *No. of xerophthalmia patients* |
|---|---|---|---|
| 0–4 | 150 | 0·7 | 1 |
| 5–9 | 97 | 0 | 0 |
| 10–14 | 126 | 4·8 | 6 |
| 15–24 | 137 | 13·1 | 18 |
| 25–34 | 237 | 3·8 | 9 |
| 35–44 | 79 | 6·3 | 5 |
| 45–54 | 42 | 2·4 | 1 |
| 55–64 | 22 | 0 | 0 |
| 65–74 | 7 | 0 | 0 |
| 75+ | 3 | 0 | 0 |

## Discussion

According to estimates[1 2] the prevalence of blindness in Africa (as defined by the WHO) is between 1·2% and 1·5%. Ocular surveys conducted throughout rural Kenya between 1976 and 1983[3] indicate a prevalence in the whole of Kenya of 0·7%. Prevalence in rural areas was 0·9%, but varied from region to region considerably. For example in the Nyeri region it was 0·3%, but in Meru it reached 1·9%. Major causes of blindness were found to be senile cataract (38% of total blindness), trachoma (19%), glaucoma (9%), and all other causes (22%). Although Sauter reported in 1976 that vitamin A deficiency was the most important cause of blindness in Kenya children,[6] this was not confirmed in later surveys.

We found the prevalence of blindness to be 1·1% in the Turkana region. This places the region (with respect to blindness prevalence) close to the Meru region, which is also a semiarid area. If we assume that the Turkana number about 200 000 people, the number of blind people (WHO definition) was 2200.

Although it is difficult to draw conclusions from such a small sample (10 people), the following facts emerge. Up to the age of 35 blindness is due mainly to corneal disease from xerophthalmia (which might have been complicated by measles, as the history of some of the people involved indicates) and trachoma. At 45 years and over blindness is due mainly to lens problems (senile cataract). Among women senile cataract was a major cause of blindness, among men trachoma. In view of the previous surveys done in Kenya xerophthalmia (which could have been complicated by measles) proved to be an unexpectedly important cause of blindness. Since the region has suffered in the past decade from several periods of drought, this may have been the result of malnutrition, which predisposes to xerophthalmia. People who suffered concurrently from measles were predisposed to develop keratomalacia and, later, blindness. No congenital blindness was found, perhaps because of the small number of people examined (900). Intraocular pressure was not measured, and therefore no blindness due to glaucoma could be identified.

### MONOCULAR BLINDNESS

The prevalence of monocular blindness was found to be 6·8%, while blindness was 1·1%. This disparity indicates the need to examine in prevalence studies, such as the one reported here, both blindness (WHO definition) and monocular blindness. Again, if we assume a Turkana population of 200 000 people, the number of sufferers from monocular blindness was 14 000. The high prevalence of phthisis (1·0%) is due to the scarcity of ophthalmic services in the area. Thus if a certain lesion such as trichiasis or entropion develops there is a high chance that it will become complicated by a secondary infection, and because of the inadequate number of ophthalmic services this could lead to blindness and phthisis.

Up to the age of 35 monocular blindness was due mainly to corneal opacities from unknown causes – 10 cases (again these could have been the result of xerophthalmia). At ages 45 and over the major cause was senile cataract (8 cases). The major difference between the causes of blindness and monocular blindness was trauma, which caused monocular blindness (13 cases) but not blindness in general.

### TRACHOMA

We found a total prevalence of trachoma of 42·8%, which means that in the whole region about 86 000 people suffer from trachoma in its various stages. There is a gradual increase in percentage of sufferers with increasing age. Of the children under 5, 33·3% suffered from trachoma. A significant increase in percentage of sufferers was noted at the age of 25 years (51·5% at the 25–34 age group). Active trachoma was most prevalent at ages under (28·7%) owing to the difficulty in maintaining hygienic conditions in this age group. Inactive trachoma began to appear at the 5–9 age group (prevalence: 18·6%). This means that there is a minimal period of five years between the active trachoma and the appearance of conjunctival scarring. At ages of 35–44, 50% of the population already have conjunctival scarring due to trachoma. Above this age there is no further increase in corneal scarring. Trichiasis and entropion begin to appear at the 25–34 age group, which means that there is minimal period of 20 years between active trachoma and the appearance of trichiasis, but once this appears corneal opacities appear concurrently.

### CATARACT

The prevalence of cataract was found to be 5·2%. This means that in the whole region there were about 10 000 sufferers. Non-traumatic cataract begins to appear at an early age (25–34), and at ages 55–64 54·5% of the population already had cataract. If we compare these results with data from India and the USA,[7 8] we see that they are closer to those of India, though cataract begins to form 10 years earlier than in India and 20 years earlier than the USA.

In previous epidemiological studies a higher prevalence of cataract was noted in women than in men.[9] This was generally ascribed to senile cataract. Although in our study a higher prevalence was noted in females (5·5% *v* 4·9%), this was related to cataract due to trauma, which is surprising, since the men are more mobile and therefore in more contact with thorny trees and bushes. Although the prevalence of traumatic cataract relative to senile cataract is relatively low (5 traumatic *v* 44 senile), this is a relatively high percentage for traumatic cataract. Traumatic cases were attributed to thorns and branches and in one case to the horn of a bull. No congenital cataract was seen. According to estimates, 1 out of 250 newborn babies suffers from some form of congenital cataract,[10] and since only 900 people were examined this could have been the reason for not finding any congenital cataract.

### XEROPHTHALMIA

A note concerning the method described for the diagnosis of xerophthalmia is appropriate here. The diagnosis of xerophthalmia is a clinical diagnosis. It was previously found that a history of night blindness is a simple and accurate tool for xerophthalmia screening.[11] We believe that the method we had employed for the diagnosis of this disease is accurate.

The prevalence of xerophthalmia was found to be 4·4%. This implies that in the whole of the region there are 8800 sufferers. According to Sommer[12] xerophthalmia becomes a public health concern when the prevalence of night blindness is above 1% (though the statistics given by Sommer relate to a population less than 5 years old). We therefore believe that xerophthalmia is a public health problem among the Turkana. Although it was expected that the maximal number of sufferers from the disease should be in the under 5 age group, we found it to be at ages 10–24. The fact that so few children under 5 were found to suffer from xerophthalmia might have been due to our method of diagnosis, that is, a history of night blindness, since it is difficult to elicit such a history from children at that age. The highest prevalence was found in the 10–24 age group among boarding school children, who presumably do not receive sufficient vitamin A. An unexpected result was a relatively high percentage of xerophthalmia in a site close to Lake Turkana where fish are abundant (6·1% of the population examined at that site), since fish liver is known to contain a large amount of vitamin A.[13] As stated the percentage of male sufferers was higher than female. This is in conformity with the known fact that more men than women suffer from xerophthalmia.[14]

### PURULENT CONJUNCTIVITIS

As expected, the highest prevalence was at ages under 5, since in this age group it is most difficult to maintain hygienic conditions. Another cluster was found at ages 45–54. The bacterial infection in all three cases was secondary to another disease such as late complications of trachoma, and was probably a chronic conjunctivitis. As to the cluster in the 25–34 age group: all three cases are primary. We have no explanation for the cluster. No cultures were taken, and therefore we do not know which types of bacteria were involved.

The findings of the survey in Turkana most probably represent the situation in other semi-arid and arid areas of developing countries. The situation should be dealt with from the start on the level of general education and environmental measures. Such an educational effort would have to take into account socioeconomic factors and various traditions. For example: unpolluted water should be supplied; in boarding schools, where avitaminosis was observed, the consumption of fruits and vegetables should be encouraged. The population should be discouraged from dependence on traditional methods in the treatment of eye diseases, which in many cases were found to do more harm than good. Above all it is essential to root out the fatalistic attitude to eye diseases which we have encountered among large segments of the population.

We believe that the number of persons suffering from ophthalmic disease, such as 10 000 cases of cataract, indicates the necessity for the permanent presence of an ophthalmologist in Turkana. Owing to the shortage of ophthalmic specialists in Kenya an arrangement should be made for one to come to the Turkana region at frequent intervals and on previously specified dates. We believe that the main problem leading to under utilisation of specialist ophthalmic help is uncertainty about the time when he is in the area. All channels of communication should be used to announce his arrival, such as communication networks of relief agencies and churches, which can also provide transport.

The survey was performed when Dr Pe'er served in Kenya on a mission of the Israeli Ministry of Foreign Affairs and the Royal Commonwealth Society for the Blind.

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# An outbreak of acute haemorrhagic conjunctivitis in Kaduna, Nigeria

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## Abstract

**Clinical studies were carried out on two groups of patients with acute haemorrhagic conjunctivitis (AHC) during an epidemic in 1985 in Northern Nigeria. Group 1 consisted of 99 students attending a girls' boarding school, group 2 of 200 patients selected randomly from 1000 examined at the local clinic.**

**Moderate to severe hyperaemia and papillary responses were present in the palpebral conjunctiva of all patients, and 234 (66%) had subconjunctival haemorrhages. Transient superficial punctate keratitis was noted in over 60% of patients. A transient flare suggestive of a low grade iritis was seen in five patients. No neurological disorders were noted.**

**Serological studies were carried out on patients from group 2. Fifteen paired and 20 single serum samples were titrated against adenovirus type 4 (Ad-4) and enterovirus type 70 (EV-70). Two pairs of sera showed a 4-fold rise in antibody levels to EV-70, whereas the antibody titres to EV-70 in the rest of the sera ranged from 1:20 (no antibody) to 1:160. None of the paired serum samples showed a 4-fold rise in antibody levels to adenovirus.**

**The results of clinical studies and serological findings support EV-70 as a probable cause of AHC in Nigeria.**

Acute haemorrhagic conjunctivitis (AHC) was first reported in Ghana, in 1969,[1,2] and was dubbed 'Apollo' disease by the local populace because it coincided with Apollo II landing on the moon. AHC epidemics were later reported in most developed and developing countries.[3] In Nigeria, AHC occurred in epidemic proportions at about the same time as it was first reported in Ghana.[4,5] Enterovirus 70, a picornavirus, has been isolated from most cases of AHC, but Coxsackie A24 and adenovirus have also been isolated during AHC epidemics.[6,7] In Nigeria attempts to isolate the cause of AHC during an epidemic in 1981 were unsuccessful, but serological tests indicated that the epidemic was probably due to enterovirus 70.[8]

We report here the results of clinical and serological studies carried out during an epidemic of AHC in Northern Nigeria in 1985. In this study no attempt was made to perform isolation tests because of the lack of facilities.

## Patients and methods

The first cases of AHC were referred from a girl's boarding school in Kaduna metropolis. A team was sent to the school to investigate, and a total of 116 students were examined. Inquiries were made as to the age, time of onset, symptoms, and conditions in the living quarters. Laterality, visual acuity, conjunctival signs, corneal involvement, preauricular lymphadenopathy, and other associated signs were assessed. At about this time an epidemic of AHC developed in the town and the adjacent districts. Of patients attending the Guinness Ophthalmic Unit of the Ahmadu Bello University with AHC one in five were selected for entry into this study. Basic epidemiological data, such as history of illness, exposure to infection and previous treatment were recorded in a special proforma. Ocular examination was carried out with a slit-lamp, and attention was paid to the location of subconjunctival haemorrhages, superficial punctate keratitis (SPK), keratic precipitates, and coalescent corneal lesions. The anterior chamber and pupils were examined, and neurological disorders were looked for. Patients were asked to return on the third day, and first, second, and third weeks after the first presentation.

### SEROLOGY

Blood was collected by venepuncture from 35 patients at first presentation and from 15 seven days afterwards. Serum was separated from these samples on the same day and kept frozen until sent to the laboratory in Britain.

### ANTIGENS

The Singapore strain (EH 91/71) and the London strain (23356/71) were used as antigens for the detection of antibodies against enterovirus type 70 (EV-70). Adenovirus type 4 (Ad-4) was used as antigen for the detection of group specific antiadenovirus antibody. Secondary baboon kidney cells (BK) were used for propagation of EV-70 strains. The single strength Wellcome 199 medium was supplemented with 10% inactivated fetal bovine serum (FBS), 0·1 g/l glucose, 25 ml/l of 4·4% sodium bicarbonate, and antibiotics (penicillin at 100 units/ml and streptomycin at 100 μg/ml). HEp-2 cells were used for propagation of Ad-4. The cells were grown in growth medium (GM), which consisted of Eagles' minimum essential medium (MEM) supplemented with glutamine, vitamins, 10% FBS, and antibiotics (vancomycin 100 μgm/ml and streptomycin 50 μgm/ml). Confluent monolayers were maintained on maintenance medium (MM), which was similar to GM but with only 3% FBS.

Monolayers of BK and HEp-2 cells in 75 cm$^2$ flasks were drained of growth medium and inoculated with 5 ml of appropriate seed of virus culture (propagated and titrated previously). The virus was adsorbed on to the monolayer for one hour at 35°C. The inoculum was removed and replaced with prewarmed fresh MM and the flasks were further incubated at 35°C. Between 50 and 75% of the cytopathic effect was usually observed within 24 to 48 hours after infection. The monolayers were then washed twice with phosphate buffered saline at pH 7·3 (PBS). Next, the cells were scraped into PBS, centrifuged at 300 g for 10 minutes at room temperature, and the pellet was finally suspended in fresh PBS to give a turbid preparation. Controls were prepared in a similar way but from uninfected cells.

The cell suspension was then dotted on glass slides with mapping pens (Joseph Gillott Co. pen no. 659). Five antigen dots consisting of (1) uninfected BK cells (as negative control); (2) BK cells infected with 23356/71; (3) BK cells infected with EH91/71; (4) uninfected HEp-2 cells (negative control); and (5) HEp-2 cells infected with Ad-4, were prepared in a cluster. Each slide contained eight clusters. The slides were dried and fixed in acetone for 10 minutes at room temperature and stored at −20°C until used.

Dilutions of test serum (1:20 to 1:640) were each applied on one cluster, and the slides were incubated in a humid chamber at 35°C for 30 minutes. The slides were then washed in PBS at pH 7·3 for 15–20 minutes, and fluorescein isothiocyanate (FITC) labelled goat antihuman IgG serum was applied as a second antibody layer and incubated as above. They were then washed in PBS for 10 minutes and for a further five minutes in deionised water. After being dried they were mounted in buffered glycerol. Each dot of antigen was examined with a Zeiss standard 18 UV microscope fitted with a filter set 10 under 400 times magnification for the presence of brightly fluorescing particulated inclusions in the cytoplasm of infected cells. The titre of the serum was defined as the reciprocal of the test dilution which gave 25–50% fluorescence. A negative and a positive control serum were always included to ensure specificity of the slide antigen.

## Results

### BOARDING SCHOOL

AHC was detected in 99 students ranging in age from 8 to 19 years. The cases were detected from at least seven different dormitories, most being from one dormitory. All the dormitories were overcrowded and short of water. It was found that the students were commonly using each others' towels, handkerchiefs, and cosmetics. AHC was bilateral in 78 cases (79%). The visual acuity was 6/6 in 125 eyes. The symptoms and signs of AHC in these students are presented in Tables 1 and 2.

*Ophthalmic clinic.* About 1000 cases of AHC presented at the clinic between July and October 1985. Two hundred consecutive cases (one in every five examined) were selected and examined in detail.

*Age and sex.* The ages of patients varied from 9 to 75 years, mean 26·4 years. Altogether there were 89 females (44·5%) and 111 males (55·5%).

*Ethnicicity.* 38·5% of the cases were Hausas, which forms the main ethnic group in the clinic's catchment area. Yorubas accounted for 16% and Nupes for 5·5%. There were nine Ibos (4·5%) and nine Idomas (4·5%). The others belonged to minority groups.

TABLE I *Symptoms at first examination in 177 infected eyes of 99 students*

| *Symptom* | *Number (%)* |
|---|---|
| Pain | 127 (72) |
| Itching | 31 (17) |
| Lacrimation | 23 (13) |
| Foreign body sensation | 23 (13) |
| Redness | 22 (12) |
| Discharge | 5 (3) |
| Reduced visual acuity | 4 (2) |
| Swelling | 2 (1) |
| Headache | 1 (0·5) |

TABLE II *Signs at first examination in 177 infected eyes of 99 students*

| *Sign* | *Number (%)* |
|---|---|
| Hyperaemia | 177 (100) |
| Papillary hypertrophy | 96 (54) |
| Subconjunctival haemorrhage | 81 (46) |
| Watery discharge | 154 (87) |
| Mucopurulent discharge | 23 (13) |
| Gross lid oedema | 7 (4) |

TABLE III *Occupational groupings in 200 AHC clinical cases*

| *Occupation* | *Number (%)* |
|---|---|
| Students | 51 (25·5) |
| Industrial workers | 49 (24·5) |
| Housewives | 41 (20·5) |
| Office workers | 34 (17) |
| Military/paramilitary | 8 (4) |
| Children | 8 (4) |
| Others | 6 (3) |
| Unstated | 3 (1·5) |

TABLE IV *Previous medication before consultation in 200 AHC clinical cases*

| *Medication* | *Number (%)* |
|---|---|
| Nil | 108 (54·0) |
| Antibiotic drops | 35 (17·5) |
| Unspecified drops | 13 (6·5) |
| Does not know | 10 (5·0) |
| Steroid containing drops | 7 (3·5) |
| Sugar water | 6 (3·0) |
| Mentholatum | 2 (1·0) |
| Hot fomentation | 1 (0·5) |
| Ice blocks | 1 (0·5) |
| Irrigation | 1 (0·5) |
| Local gin | 1 (0·5) |
| Atropine | 1 (0·5) |
| Yeast tablets | 1 (0·5) |
| Unstated | 13 (6·5) |

TABLE V *Main symptoms in 200 AHC clinical cases*

| *Complaint* | *Number (%)* |
|---|---|
| Discharge | 195 (97·5) |
| Foreign body sensation | 182 (91·0) |
| Pain | 170 (85·0) |
| Blurred vision | 84 (42·0) |

*Occupation.* Distribution of AHC in relation to occupation is shown in Table 3. Although the Nigerian population is predominantly agrarian, only one farmer was seen with AHC. Five patients belonged to the executive/managerial group, suggesting that the disease was mainly confined to workers with low income.

*Previous treatment.* Ninety-two (46%) of the two hundred patients had received topical medication prior to consultation. The drugs were obtained mainly from chemists, dispensaries, and shops without prescription. The types of medication used are shown in Table 4. One patient had applied a mixture of locally brewed gin, 'ogogoro', and sugar water, ending up with severe corneal melting and corneal vascularisation.

*Previous conjunctivitis.* In 136 (68%) of the patients a previous history of severe conjunctivitis was reported.

*Incubation period.* The incubation period varied widely, but about 55% of cases had contracted the disease within one week of exposure.

*Laterality.* One hundred and forty patients (70%) attended the clinic by the second day of the onset of conjunctivitis. The condition was bilateral in 154 (77%) cases and unilateral in 46 (23%) cases. In 132 (86%) of the bilateral cases the second eye developed infection within 24 hours of the first eye. For the rest it varied from two to seven days.

*Symptoms.* The main symptoms are shown in Table 5.

*Signs.* The main clinical signs are shown in Table 6. Of 354 infected eyes 250 (70·6%) had a visual acuity of 6/9 or better. In 23 patients the vision was less than 6/60. The causes of visual defects in these patients are shown in Table 7. Moderate to severe hyperaemia and papillary responses were present in the palpebral conjunctiva of all patients, and 234 (66%) had subconjunctival haemorrhages.

In 189 (53·4%) of the affected eyes the corneal involvement was usually in the form of superficial punctate keratitis, and in 20 (5·7%) coalescent corneal erosions were present. Anterior chamber flare was found in association with AHC in five cases. The flare resolved following improvement in the conjunctivitis. Complications due to secondary bacteria was not noted.

*Treatment.* Most of the patients were treated with sulphacetamide 10% eye drops four times a day and terramycin eye ointment at night. This was aimed at preventing secondary bacterial infection. Treatement was usually as an outpatient, but patients who had corneal lesions due to noxious topical self-medication were admitted to the hospital.

*Follow-up.* Only 69 patients came back after the first visit. Of the 40 patients seen on the third day only one was totally cured. Thirty-seven patients were seen after one week, of whom 12 (32%) were cured. Eleven still had SPK, six had haemorrhages, and four complained of foreign body sensations. Thirteen patients were seen during the second week, of whom eight (61%) were cured. One patient still had SPK, one complained of itching, and one of lacrimation. The others had minor symptoms. Only four patients came back for the third week follow-up. All were virtually cured except for one who had residual follicles.

### SEROLOGY

Paired sera were collected from 15 patients. Twenty single serum samples were also collected during the visit.

The antibody levels to EV-70 and adenovirus in the 35 sera collected at the first visit ranged from <1:20 (no antibody) to 1:160 (Table 8). It was interesting to note that sera which had a titre greater than 1:40 to EV-70 had a titre of <1:20 to adenovirus and vice versa. There was no significant difference between the antibody response to the London or the Singapore isolate of EV-70 in 15 paired serum samples (Table 9). Two pairs of sera showed a 4-fold rise from <1:20 to 1:40, whereas four pairs of sera showed a 2-fold rise in titre to EV-70. The rest of the pairs showed no rise in antibody titres. Only one pair of serum samples had a 2-fold rise in antibody levels to adenovirus.

A 4-fold or greater rise in antibody titre or a static titre greater than 1:40 to EV-70 was considered to indicate a recent infection. Hence the two pairs of sera which had a 4-fold rise in titre to EV-70 and the six sera which had a titre greater than 1:40 to London isolate were regarded as positive. The four sera which had a titre greater than 1:40 to Singapore isolate of EV-70 had the same levels of antibodies to the London isolate of EV-70. All the sera were put through the test system a second time to confirm the results obtained initially.

TABLE VI *Clinical signs in 354 affected eyes of 200 patients*

| *Signs* | *Number (%)* |
|---|---|
| Bulbar Hyperaemia | 335 (94·6) |
| Discharge | 291 (82·2) |
| – Watery | 159 (44·9) |
| – Watery + mucopurulent | 180 (50·8) |
| – Mucopurulent | 84 (23·7) |
| Subconjunctival haemorrhage | 234 (66·1) |
| – Generalised | 127 (35·9) |
| – Superior fornix | 104 (29·4) |
| – Nasal | 2 (0·57) |
| – Temporal | 1 (0·28) |
| Superficial punctate keratitis | 189 (53·4) |
| Gross chemosis | 56 (15·8) |
| Preauricular lymphadenopathy | 24 (6·8) |
| Gross lid oedema | 19 (5·4) |
| Coalescent corneal erosions | 20 (5·7) |
| Anterior chamber flare | 5 (1·4) |

TABLE VII *Causes of visual defects in 23 patients with AHC*

| *Findings* | *Frequency* |
|---|---|
| Pre existent corneal opacities | 8 |
| Adherent leucoma | 4 |
| Pterygia | 4 |
| Cataracts | 3 |
| Disc pallor | 2 |
| Phthisis bulbi | 1 |
| Aphakia | 1 |

TABLE VIII *Detection of antibody titres to Ad-4 and enterovirus type-70 (23356/71 and EH91/71) in 35 serum samples collected during the first visit*

| *Reciprocal* | *No. of patients* | | |
|---|---|---|---|
| *Antibody titre* | *Ad-4* | *23356/71* | *EH91/71* |
| <20 | 15 | 11 | 12 |
| 20 | 7 | 10 | 10 |
| 40 | 7 | 8 | 9 |
| 80 | 4 | 4 | 3 |
| 150 | 2 | 2 | 2 |
| Total | 35 | 35 | 35 |

TABLE IX *Detection in rise of antibody titres to adenovirus type 4 (Ad-4) and enterovirus type 70 (i) EV-70/23356/71; (ii) EV-70/EH91/71) in 15 paired serum samples*

| | *No. of serum pairs* | | |
|---|---|---|---|
| *Rise in Ab titre* | *Ad-4* | *23356/71* | *EH91/71* |
| None | 14 | 9 | 9 |
| 2-fold | 1 | 4 | 4 |
| 4-fold | 0 | 2 | 2 |
| Total | 15 | 15 | 15 |

## Discussion

The sequence of events during the epidemic of AHC in Northern Nigeria in 1985 indicates that the epidemic may have started in the girl's boarding school in Kaduna and from there spread rapidly to the urban population. By early 1986, the epidemic had extended to Southern Nigeria. At the school, AHC spread rapidly owing to over-crowding of the dormitories, inadequate sanitation, shortage of water, and the unhygienic habits of the students. Following the first examination and at the height of the epidemic the students were sent home because it was the end of the school term. The release of infected students into the community was probably responsible for the community outbreak of AHC.

Students, industrial workers, housewives, and office workers formed the main groups of people who acquired the infection. Only one patient was from the rural area. The Guinness Ophthalmic Clinic is the only well established 'public' eye clinic in Northern Nigeria, and it serves a large number of villagers with ophthalmic problems, including conjunctivitis. Hence either the AHC epidemic was mainly restricted to the urban population with no sizeable epidemic in the relevant rural population, or villagers with AHC did not attend the clinic.

The clinical feature and severity of AHC observed in our patients were very similar to those reported elsewhere[1-5] except for the presence of SPK in 56·4% of the cases compared with 3·9% reported in an earlier episode of AHC.[8] Coalescent corneal erosions were observed in 5·9% of the total cases. The erosion was limited and did not affect vision. During the short period of follow-up in our patients we did not see any evidence of neurological manifestation. Neurological disorders have been reported during epidemics of AHC, particularly in Asia.[9]

The adverse effect of self-medication on the prognosis of AHC has been reported previously.[10] About 46% of the patients we saw had been treated previously. One patient had applied a mixture of locally brewed gin ogogoro and sugar water. This resulted in severe corneal melting and corneal vascularisation.

Serological studies, especially tests for neutralising antibodies, have been used extensively to investigate the role of EV-70 as the causative agent of AHC. The tests are particularly useful where facilities for isolation of EV-70 do not exist. This was experienced during an outbreak of AHC in 1981 in India[11] and Zaire.[12]

Fifteen paired and 20 single serum samples were available for serological studies. In our laboratory we have found a good correlation in antibody levels to EV-70 in sera by using either a neutralisation method or an indirect immunofluorescence test (unpublished data). The antibody response to the London isolate and the Singapore isolate of EV-70 was not significantly different. Only two pairs of sera showed a 4-fold rise in antibody levels to EV-70, whereas the titres to EV-70 in the rest of the sera ranged from 1:20 to 1:160. This made it rather difficult for us to interpret the results. Neutralising antibody levels of 1:16 or greater to EV-70 in convalescent sera has been considered to be a critical diagnositic level.[13] However, neutralising antibody titres from 1:16 and 1:64 against EV-70 have also been shown to persist in sera for up to 21 months.[21] Hence, there is always a possibility that the presence of these antibodies may have been due to a previous exposure to the agent. In 136 (68%) of our patients a previous history of severe conjunctivitis was reported. We therefore considered a titre of greater than 1:40 as a good indicator of recent infection.

The sera were also screened for the presence of antibody levels to adenovirus. None of the paired serum samples showed a 4-fold rise in antibody. Six sera (three paired serum samples) had a static titre greater than 1:40 to adenovirus. This could be due to a previous exposure to ocular or pharyngeal infection with adenovirus. There is also a possibility that these three patients were cases of adenovirus ocular infection which were clinically indistinguishable from that of EV-70.

Many epidemiological and laboratory problems associated with the study of epidemics of acute haemorrhagic conjunctivitis still remain unsolved. Perhaps the development of more sensitive culture tests for the isolation of causative agents or direct methods for the detection of virus in clinical specimens, along with complementary serological tests, will help us to understand epidemics of acute haemorrhagic conjunctivitis.

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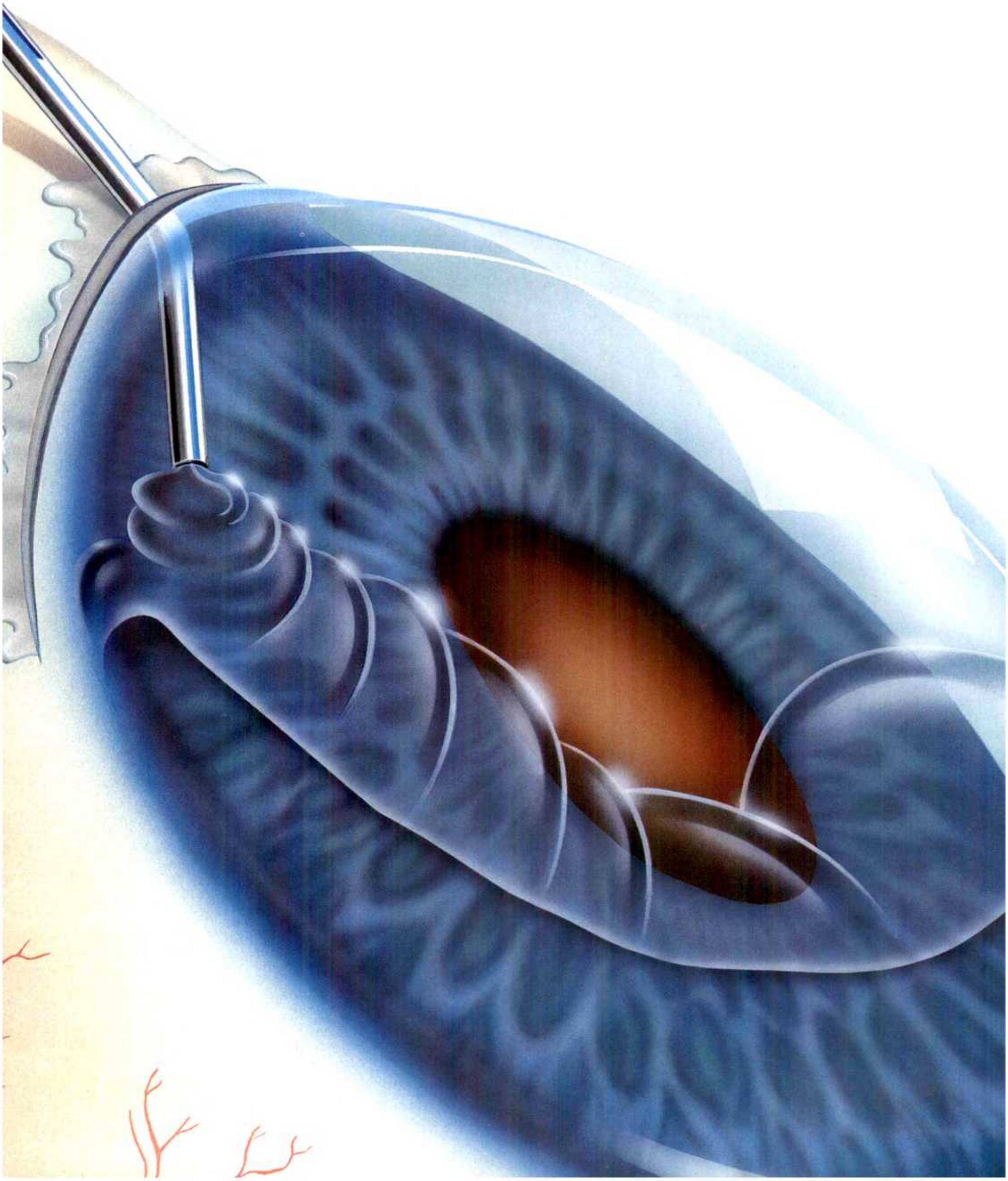

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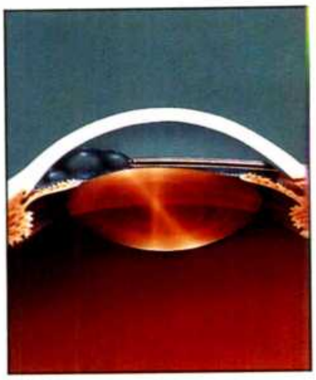

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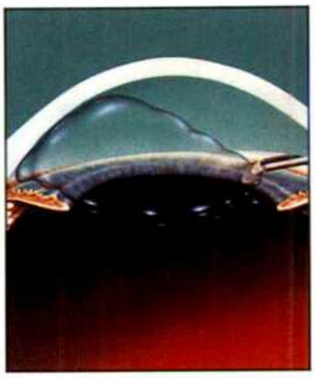

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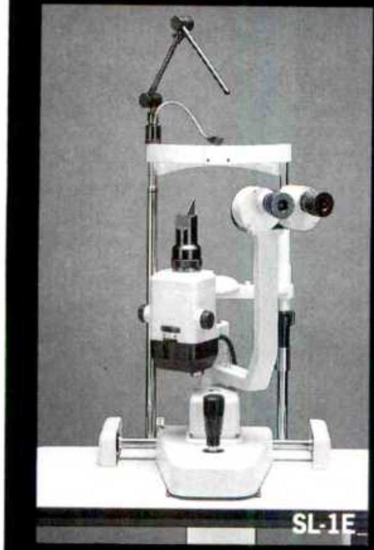

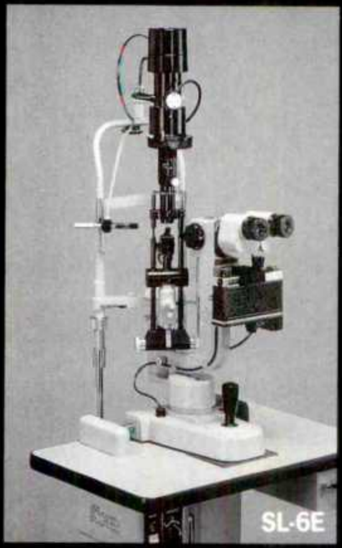

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# Chorioretinal neovascular membranes complicating contusional eye injuries with indirect choroidal ruptures

C M Wood, J Richardson

## Abstract

**Chorioretinal neovascular membranes are a recognised but rare cause of late visual loss in eyes suffering contusional injuries. A series of eight cases is presented all with indirect choroidal ruptures involving the perifoveal region. Two main patterns of 'at risk' rupture were noted: a temporally situated rupture passing almost directly through the fovea, and a rupture which curves inferior or superior to the optic disc stopping just short of the fovea. In six of eight cases there was only a partial thickness rupture of the choroid. These neovascular membranes may present at any time after the original injury, either early (within six months of the injury), which could be related to persistence of the normal reparative neovascular response, or late (at least one year after the injury), which are more likely to have resulted from a secondary breakdown of the outer blood-retina barrier.**

Late visual loss following a contusional eye injury may result from retinal detachment, angle recession glaucoma, or the growth of a chorioretinal neovascular membrane (CRNVM).[1-3] CRNVM formation is a rare complication which usually occurs in eyes with perifoveal[4] indirect choroidal ruptures (ICR), the overall rate of development of CRNVM in ICR being less than 5%.[1 4] While in some cases substantial loss of central vision occurs, many follow a remarkably benign course compared to CRNVM in senile macular disease.[4-6] In certain cases, however, laser treatment has appeared to be beneficial.[4 7-10]

This is a report on eight patients who developed a CRNVM as a complication of a perifoveal ICR and a review of the literature on the subject. The two main aims of the study were: (1) to see if we could identify the specific type or types of ICR which are likely to develop a CRNVM; (2) to find if there is a specific time interval between the injury and the onset of a CRNVM.

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## Materials and methods

Patients were included in this study if they had an ICR following a non-penetrating eye injury, with clinical and angiographic evidence of the CRNVM. Six out of eight patients had hospital records available from the time of the original injury. The other two patients could accurately date their eye injury. All patients had a full ophthalmic assessment, including biomicroscopy of the anterior and posterior segment, indirect ophthalmoscopy, retinal photography, and fluorescein angiography. For each patient the time interval between the injury and either the onset of symptoms of the CRNVM or the finding of clinical or angiographic evidence of a CRNVM was noted. A total of eight patients with a CRNVM developing as a result of an ICR were recruited for the study. A composite diagram was constructed which outlined the site of each rupture which had developed a CRNVM by projecting individual fundus photographs on to a screen. For ease of comparison all slides were projected as if they were a left eye.

## Results

Of the eight patients recruited for the study six were male and two female, with an age range of 18–45 years and a follow-up time of 15–72 months. The age at the time of the injury and the time interval between the injury and the onset of the CRNVM are shown in Table I. Four cases developed the CRNVM within four months of the injury. In the other four cases the CRNVM occurred between 20 months and 37 years after the injury. The time delay between injury and CRNVM is also shown in Table II, which includes a review of the literature.[1 3 5 7-15] Although this table divides the patients by the time delay into three groups, <6 months, 6–12 months, and >1 year, most cases fell into the <6 months (early onset) or >1 year (late onset) groups.

All eight ICR are illustrated in the composite diagram (Fig 1). Two main patterns emerge: *type*

TABLE I *Summary of clinical details of patients developing a CRNVM as a complication of a contusional eye injury*

| *Case* | *Age at injury (years)* | *Injury to CRNVM (months)* | *Initial VA* | *Final VA* | *Site* | *Other factors* |
|---|---|---|---|---|---|---|
| 1 | 29 | 2 | 6/5 | 2/60 | Temporal | |
| 2 | 20 | 4 | 6/6 | 6/6 | Inferior | |
| 3 | 36 | 15 years | 6/6 | 6/60 | Superior | Diabetic |
| 4 | 39 | 20 | 6/6 | 3/60 | Superior | Detachment |
| 5 | 37 | 8 years | 6/9 | 6/9 | Inferior | |
| 6 | 36 | 4 | 6/12 | 6/18 | Temporal | |
| 7 | 8 | 37 years | 6/60 | 6/60 | Temporal | |
| 8 | 18 | 4 | 3/60 | 2/60 | Temporal | Hypotony |

TABLE II *Time interval between initial injury and development of a CRNVM in our series (first set of figures) and in series reported elsewhere (figures in brackets)*

| *Time from injury to CRNVM* | *No of patients* |
|---|---|
| Less than 6 months | 4 (17) |
| 6 to 12 months | 0 ( 5) |
| More than 1 year | 4 (13) |

The numbers in brackets refer to reported cases[1 4 5 7-15] combined with our series.

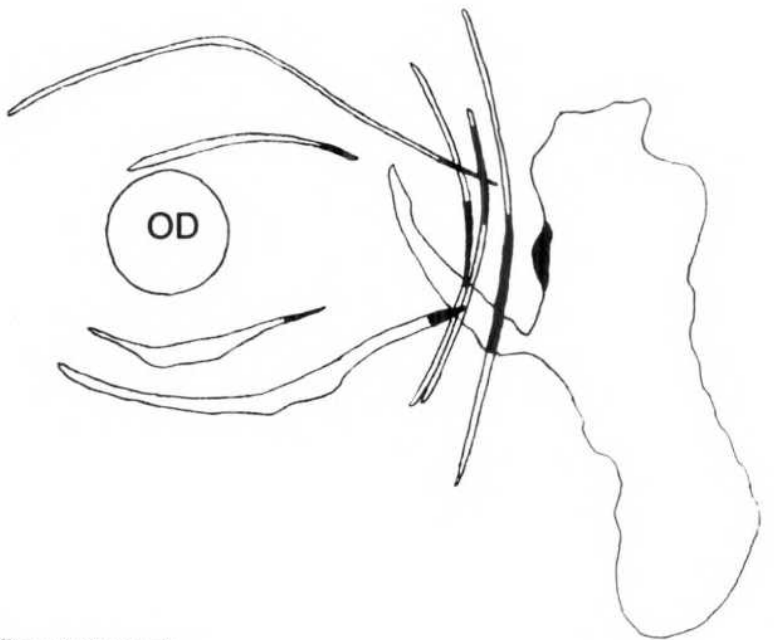

*Figure 1: Composite diagram illustrating sites of individual ICR developing CRNVM. Black areas are the actual site of the neovascular membrane.*

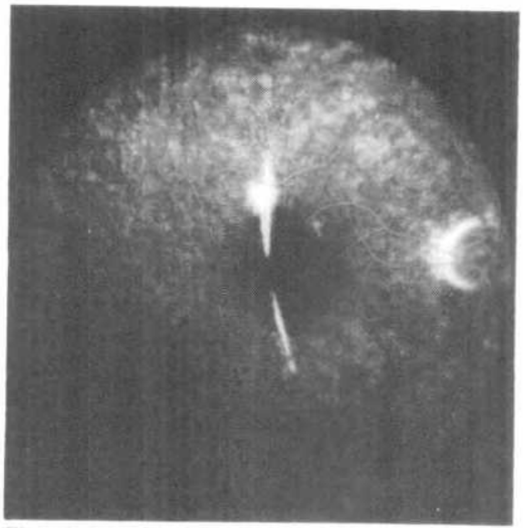

*Figure 2: Late phase fluorescein angiogram of patient 1 six weeks after injury. CRNVM present but is asymptomatic (? persistence of normal reparative choroidal neovascularisation in a dormant stage). Visual acuity 6/5.*

*1* temporally situated passing through the fovea; and *type 2*, inferior/superior to disc with apex near fovea.

Fluorescein angiograms of typical type 1 (Figs 2, 3, 4) and type 2 (Figs 5, 6) ICR with CRNVM are illustrated. As can be seen from the angiograms, these ICR are mainly very thin, partial thickness ruptures. Figure 6 is an exception, being a broader, mainly full thickness rupture; however, it is at the thin apex, which extends into the perifoveal region, that the CRNVM developed. The other broad full thickness rupture in the series was an unusual case in that the CRNVM developed 37 years after the injury and was very similar in appearance to another late onset CRNVM (26 years after injury) described by Yanuzzi *et al.*[15]

In three eyes complicating factors were present, which may have influenced the development of a CRNVM. Patient 3 was a diabetic with an ICR above the disc and had inferotemporal laser for peripheral new vessels. Two months later a CRNVM occurred related to the ICR. There was no damage to the ICR from the laser, nor was there any significant diabetic maculopathy. Patient 4 had a retinal detachment due to a dialysis which occurred before the CRNVM. Patient 8 had prolonged hypotony, which produced disc swelling (Fig 7) and macula oedema and later developed glaucoma.

The visual outcome is displayed in Table I and Figure 8. Three eyes with good vision maintained this without treatment (patients 2, 5, 6). Three patients with initially good vision had their vision reduced to 6/60 or less (patients 1, 3, 4), one having unsuccessful laser therapy for the CRNVM and another losing central vision owing to a retinal detachment. Two patients with initially poor vision were unchanged. The time of onset or type of rupture did not affect the visual outcome.

## Discussion

Following contusional eye injuries the retinal pigment epithelium (RPE) and Bruch's membrane (BM) are particularly at risk of damage, and the outer blood-retina barrier breaks down in response to this insult.[1 14 16] This primary breakdown is usually restored to normal within

*Figure 3: Patient 1 six months after injury. CRNVM is now symptomatic and is a growth phase. (a) Early phase. (b) Late phase.*

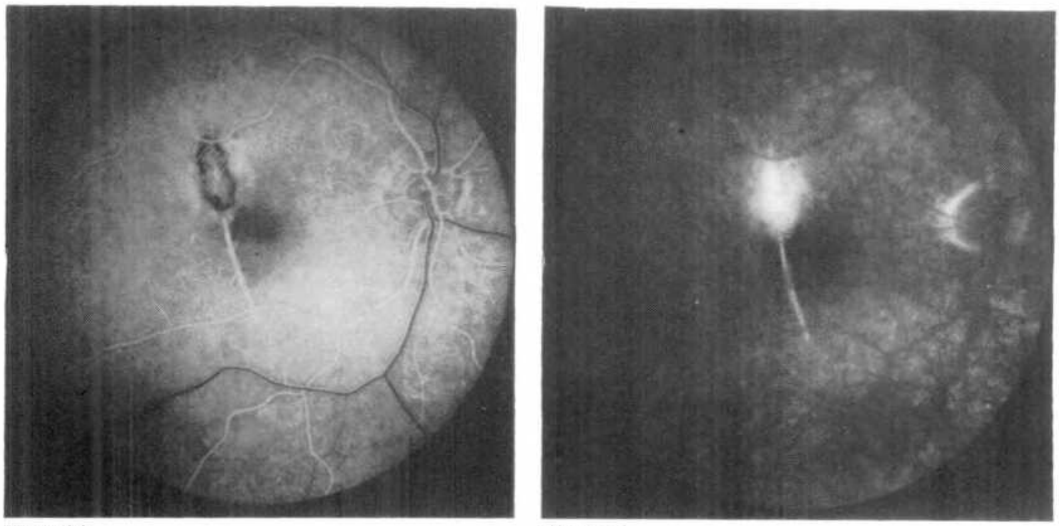

*Figure 3A*

*Figure 3B*

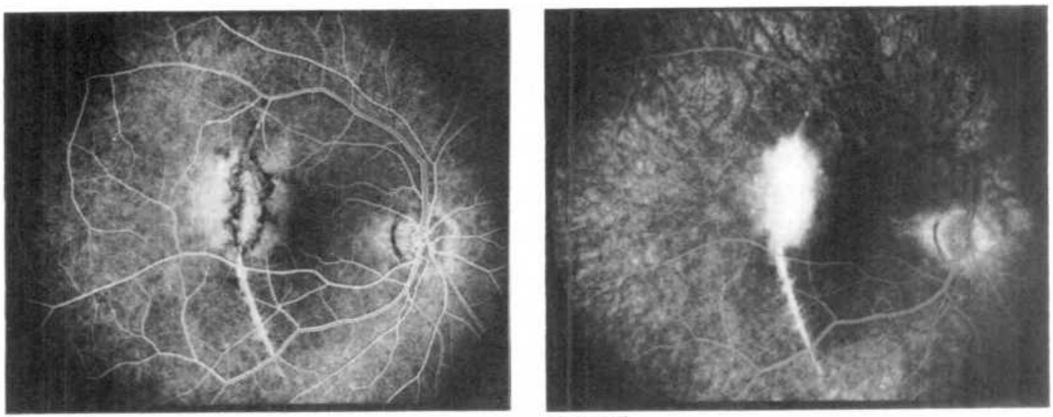

*Figure 4: Fluorescein angiogram of temporally situated ICR with CRNVM occurring four months after injury. (a) Early phase. (b) Late phase.*

*Figure 4A*

*Figure 4B*

7–14 days of the injury.[16] Histopathological studies in eyes with choroidal ruptures have shown that choroidal neovascularisation occurs as part of the repair process, generally regressing completely in the early postinjury stage.[17] Whether an exuberant overgrowth of this normal reparative choroidal neovascularisation or a persistence of this membrane in a dormant asymptomatic[18 19] phase under the RPE is responsible for the early type of CRNVM is open to speculation. Late onset CRNVM (more than one year after the injury) could also arise from a dormant choroidal neovascular membrane. However it would seem more likely, especially in cases occurring many years after the injury, that these represent a new CRNVM developing in an area of weakness – perhaps constituting a form of involutional macular degeneration due to localised, excessive 'wear and tear' following the trauma.

We noted two distinct patterns of rupture which gave rise to a CRNVM both in our series and in the majority of the reported cases[1 3-5 7-15 20]: (1) thin partial thickness ICR situated temporally and curving through the fovea; (2) ICR superior or inferior to the disc stopping just short of the fovea.

With thin, partial thickness ICR the CRNVM can develop at almost any point on the rupture, though it is usually near the fovea. If the ICR is broad and full thickness, a CRNVM is most likely to develop if the apex of the rupture extends into the perifoveal region, and the CRNVM would then occur at the foveal end.

The predilection of CRNVM for the macular region is well established in other diseases[6 21] and presumably accounts for the perifoveal situation of most CRNVMs associated with ICRs. The neovascular inhibitory ability of the RPE is least in the perifoveal region and appears to decline with age.[21] Consequently ruptures of BM and damage to the RPE are much more likely to result in a CRNVM in this site than at other areas in the retina.[22]

The final visual outcome in these eyes was relatively good, if we remember that most had no treatment. The benign nature of these CRNVMs is attributable to the fact the majority of contusional eye injuries occur in young males[23] with healthy RPE. Furthermore the type of rupture which gives rise to a CRNVM often produces a very focal area of damage; therefore the ICR is surrounded by a zone of healthy RPE functioning as normal to inhibit angiogenesis.[24] Presumably CRNVMs arise at sites where a balance has been achieved, such that the damage to the RPE and Bruch's membrane is sufficient to prevent them from performing their normal task of inhibiting subretinal neovascularisation, while the damage incurred by the choriocapillaris is insufficient to prevent it from proliferating through any gaps created.

It is worth noting that 'other factors' (laser for diabetic retinopathy, retinal detachment, hypotony) may have played a part in the development of the CRNVM in three out of eight

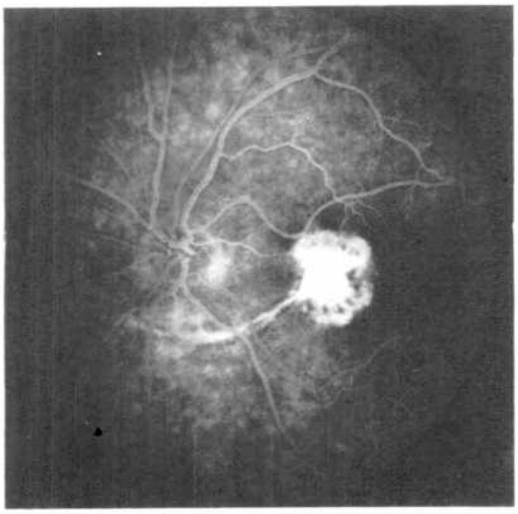

*Figure 5: Patient presenting with visual distortion. Fluorescein angiogram shows ICR inferior to disc with CRNVM at foveal end. History of contusional injury eight years previously (punch) given only in retrospect. Symptoms settled without treatment, maintaining 6/9 vision.*

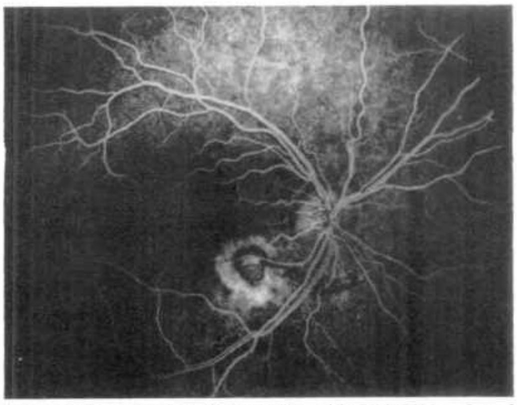

*Figure 6: Broad ICR inferior to disc with CRNVM at foveal end. Visual acuity maintained at 6/6.*

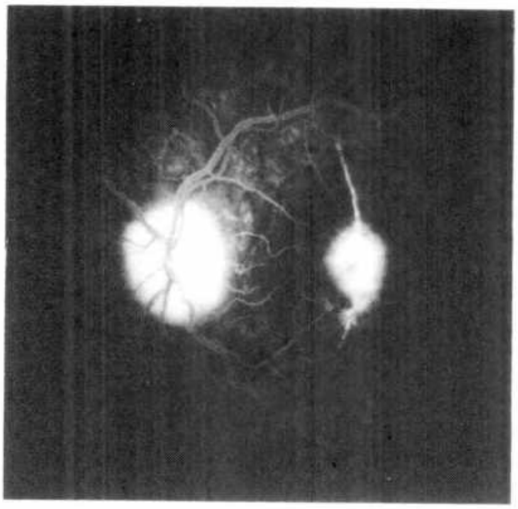

*Figure 7: Swollen optic disc due to prolonged hypotony in eye with ICR and traumatic cyclodialysis cleft. Subfoveal CRNVM developed four months after injury.*

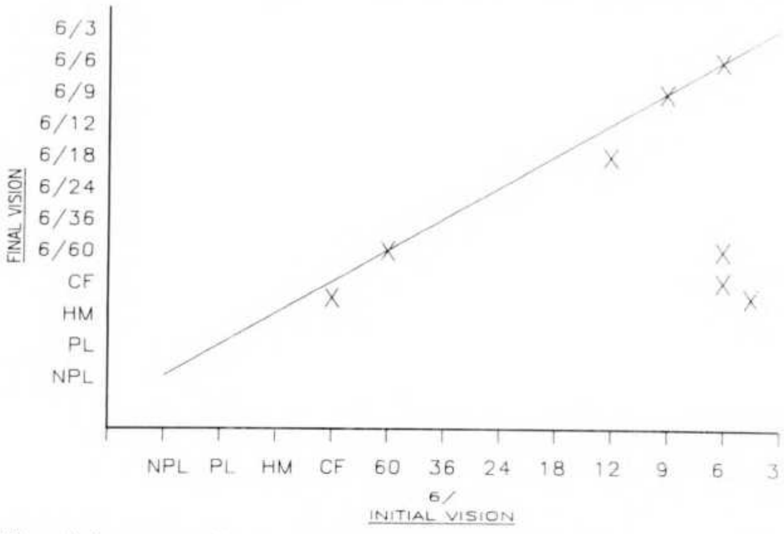

*Figure 8: Scattergram of visual acuity changes in eight eyes with ICR and CRNVM.*

of the patients, a possible link being macular oedema. Either the swelling due to the presence of extracellular fluid, which would provide spaces in the retina into which the CRNVM could grow,[25] or subtle changes at a cellular level could have been the precipitating factor in these 'at risk' eyes. Moreover, in the cases of retinal detachment and diabetic retinopathy, retinal ischaemia, which has been shown to be a factor in CRNVM formation, may have had an influence.[25]

Although disciform scar formation with central loss of vision is not an inevitable outcome in these eyes,[4 5 7] we believe that, if an eye has been identified as having an 'at risk' rupture, a fluorescein angiogram should be performed once the retinal haemorrhage has cleared. Not only does this act as a baseline which will help the interpretation of any later changes, but occasionally an asymptomatic membrane may be detected, which would then require frequent re-examination. All these patients should be warned of the symptoms of a CRNVM and closely followed up for the first six months after the injury, as it is during this period that they are most at risk of developing a neovascular membrane. However, in view of the possibility of spontaneous regression, and occasional difficulties in accurately identifying the CRNVM,[4] laser treatment is justified only after a period of observation. Finally it is worth bearing in mind that an apparently idiopathic CRNVM may actually be related to previous trauma.

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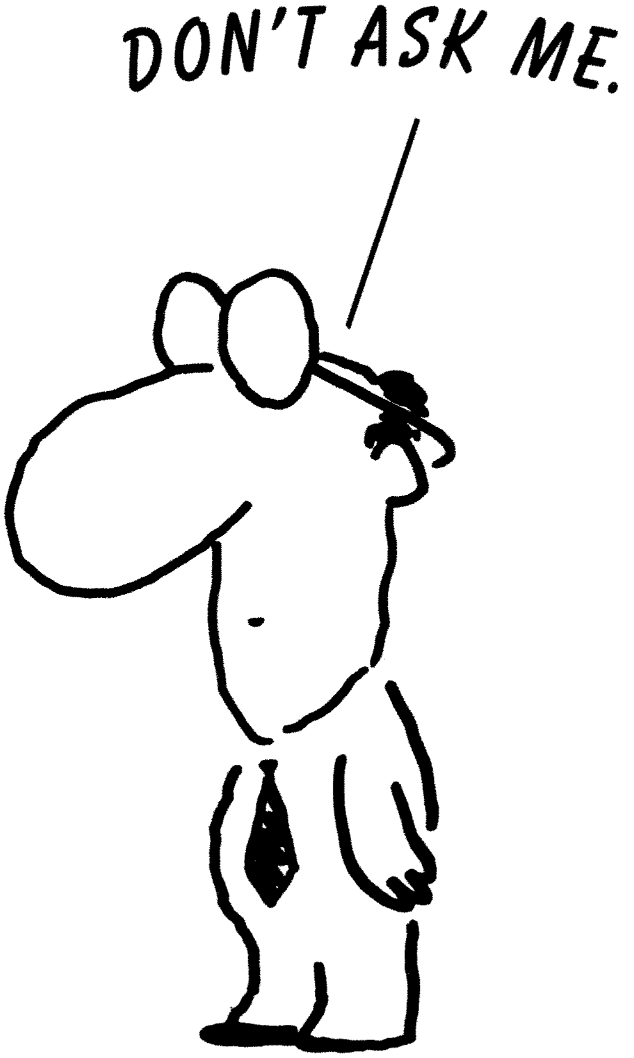

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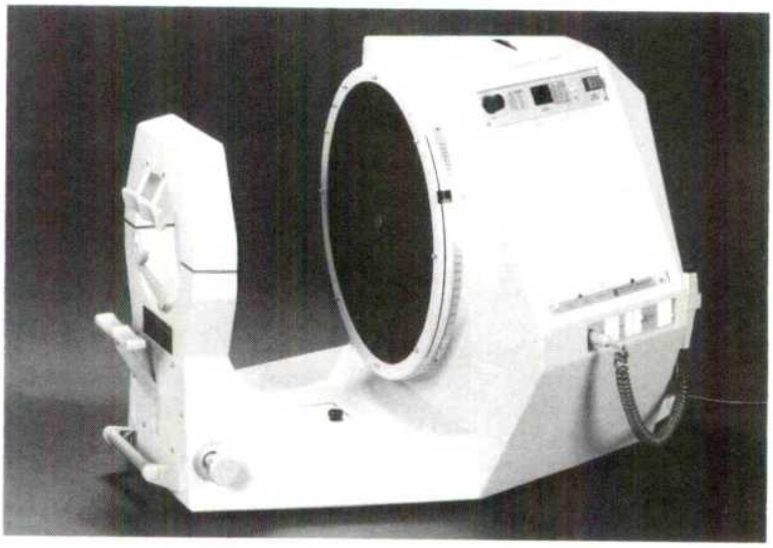

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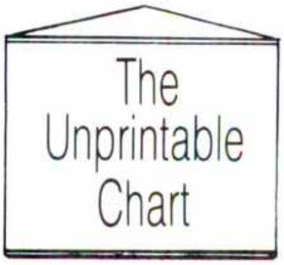

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# Orbital recurrence of retinoblastoma successfully treated by combined therapy

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## Abstract

**Five children with an orbital recurrence of retinoblastoma have been successfully treated by a combination of excision biopsy of the tumour mass, radical orbital radiotherapy, and systemic chemotherapy. Nine previous children, consecutive with the five presented here, died from disseminated retinoblastoma after failure of earlier treatment programmes for orbital recurrence. An aggressive therapeutic approach is justified by this improvement in survival.**

Orbital recurrence of retinoblastoma after enucleation has carried a poor prognosis, with the mortality rate ranging from 94 to 100% and a mean survival of 14 months.[1 2] Deaths occur from the effects of direct extension into the central nervous system and from metastatic disease. Recommended treatment now includes local surgical excision of the recurrent orbital tumour with radical orbital radiotherapy and systemic chemotherapy.[1] We report on five children successfully treated in this manner (for summary of details see Table I).

## Case reports

### CASE 1

In July 1980 a 17-month-old girl was referred with a squint of recent onset and right leucocoria. An examination under anaesthetic (EUA) revealed bilateral multifocal retinoblastomas. The right eye was enucleated in view of the size of the tumours in this eye. Histological examination showed a poorly differentiated retinoblastoma with evidence of choroidal invasion but no optic nerve involvement.

At a routine follow-up EUA 18 months after enucleation a mass was found in the right socket. Excision biopsy confirmed this to be an orbital recurrence of retinoblastoma. Routine staging investigations including chest x ray, technetium bone scan, bone marrow aspirate, cerebrospinal fluid cytology, and CT head scan showed no evidence of extraorbital spread. The patient was treated with radical orbital radiotherapy to a dose of 50 Gy in 26 fractions over 40 days and with intravenous vincristine and cyclophosphamide chemotherapy. She has been off treatment for over seven years and remains disease free.

TABLE I *Summary of cases*

| *Case* | *Sex* | *Age at diagnosis of RBL (months)* | *Interval from enucleation to recurrence (months)* | *Disease status (time off treatment in months)* |
|---|---|---|---|---|
| 1 | F | 17 | 18 | CR (84) |
| 2 | F | 92 | 8 | CR (38) |
| 3 | F | 72 | 3 | CR (27) |
| 4 | M | 19 | 9 | CR (24) |
| 5 | F | 5 | 6 | CR (8) |

RBL=retinoblastoma. CR=complete remission.

### CASE 2

In March 1985 a 7-year-old girl presented with a right panuveitis and secondary glaucoma. Medical treatment failed, and four months after presentation she underwent cyclocryotherapy, lensectomy for secondary cataract, and biopsies of some iris nodules and a white friable mass at the inferior ora serrata. These indicated a diagnosis of retinoblastoma, and the eye was enucleated.

Eight months after enucleation the patient was referred to this centre with a right orbital mass. A recurrence of retinoblastoma was confirmed by excision biopsy. Staging investigations were negative for metastatic retinoblastoma, and she received orbital radiotherapy to a dose of 44 Gy in 22 fractions over 30 days together with systemic chemotherapy with vincristine, cyclophospamide, cisplatinum, etoposide (OPEC protocol), and intrathecal methotrexate. She has been off treatment for over three years and remains well and disease free.

### CASE 3

A 6-year-old girl was noticed to have right leucocoria in July 1986. Coats's disease was suspected, and a transcleral biopsy was performed. Histological examination revealed a retinoblastoma, and the eye was enucleated. Extension of necrotic tumour tissue through the biopsy site was noted.

The patient was referred to this centre three months later with a right orbital mass. Excision biopsy of the lump confirmed an orbital recurrence of retinoblastoma, and systemic staging investigations showed no evidence of metastatic spread. The patient was treated by orbital radiotherapy to a dose of 45 Gy in 23 fractions over 37 days and received systemic chemotherapy according to our OPEC protocol together with intrathecal methotrexate. She remains disease free 27 months off treatment.

### CASE 4

A 2½-year-old boy was referred in January 1987 with a suspected orbital recurrence of retinoblastoma nine months after a left enucleation and insertion of a Castroviejo implant. The enucleated specimen showed no evidence of transcleral or optic nerve spread. On examination a diffuse mass was detected anterior to the implant which was calcified on orbital CT scan.

Excision biopsy of the mass provided histological confirmation of the diagnosis of recurrent orbital retinoblastoma, but subsequent staging investigations showed no evidence of extraorbital spread. The patient underwent radical orbital radiotherapy to a dose of 40 Gy in 20 fractions over 28 days together with systemic and intrathecal chemotherapy. He remains disease free two years after completion of treatment.

### CASE 5

A 5-month-old girl developed a right convergent squint and leucocoria in December 1987. Unilateral retinoblastoma was diagnosed and the right eye was enucleated. Histologically the resected end of the optic nerve was free from tumour, but a cluster of tumour cells was found round a vessel in the sclera on sectioning.

Six months after the enucleation the patient was referred to this centre with a swelling of her right upper eyelid. Following excision biopsy and routine staging investigations a diagnosis was made of orbital recurrence of retinoblastoma with no extraorbital spread. Orbital radiotherapy was limited to 34 Gy in 17 fractions over 26 days by a marked skin reaction. She received adjuvant systemic and intrathecal chemotherapy. There is no evidence of disease on follow-up eight months after completion of therapy.

## Discussion

In a previous study from the Paediatric Ocular Oncology Units of St Bartholomew's and Moorfields Eye Hospitals 10 patients were described who had no evidence of extraorbital spread at the time of diagnosis of orbital recurrence of retinoblastoma.[1] Of these 10 the first nine died from disseminated retinoblastoma. The tenth patient was treated by excision biopsy of the orbital recurrent tumour, radical orbital radiotherapy, and systemic chemotherapy. She is the index patient of the present series (case 1).

In our previous reported study[1] distant relapse was by far the commonest cause of death following orbital recurrence of retinoblastoma, and this was also found in Reese's series of 25 patients, none of whom survived despite treatment by orbital exenteration and radical orbital radiotherapy.[3]

In our previous study[1] three out of four exenterations for orbital recurrence were found to be incomplete histologically. One child, who received chemotherapy but no radiotherapy after incomplete exenteration, died from direct intracranial extension of retinoblastoma despite having no evidence of widespread tumour on representing with an orbital recurrence.[1] After the survival of case 1 the next four patients to present with an orbital recurrence were treated in a similar way. The success of the new therapeutic approach may be justified by the fact that nine consecutive deaths after previous treatment methods have been followed by five consecutive survivors from recurrent retinoblastoma in the orbit when we adopted a more aggressive regimen. To date, where treatment failed, all deaths from orbital recurrence have occurred within two years and most within one year. Four out of the five patients treated with our new regimen have survived more than two years and are hopefully cured.

We would suggest that orbital exenteration is unlikely to achieve complete surgical clearance of all recurrent tumour, radical orbital radiotherapy will not prevent the development of metastatic diseases, and that chemotherapy alone cannot eradicate residual orbital disease. Accordingly we would recommend that simple excision biopsy of the orbital tumour mass should be performed and that this should be combined with radical orbital radiotherapy and systemic chemotherapy.

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# Anterior ischaemic optic neuropathy and intraocular pressure

B Katz, R N Weinreb, D T Wheeler, M R Klauber

**Abstract**

**Anterior ischaemic optic neuropathy is a stroke syndrome of the distal optic nerve, characterised by disc oedema and optic nerve dysfunction – loss of central vision, loss of colour vision, a relative afferent pupillary defect, and nerve fibre layer field loss. We prospectively evaluated the changes of intraocular pressure throughout the day in 16 patients with non-arteritic anterior ischaemic optic neuropathy and 15 normal control subjects of similar age and race. The peak intraocular pressure exceeded 21 mm Hg in five of the ischaemic optic neuropathy patients but none of the controls. The mean peak intraocular pressure was 19·9 mm Hg for the ischaemic optic neuropathy group versus 17·6 mm Hg for controls (p=0·034). The range of intraocular pressure was also greater for the ischaemic optic neuropathy group (p =0·030). Eight of 16 ischaemic optic neuropathy patients had a range of intraocular pressure of 6 mm Hg or more, compared with three of 15 control subjects. The intraocular pressure exceeded 21 mm Hg during a subsequent visit in two additional patients in whom the hourly determined intraocular pressure peaked at less than 21 mm Hg. Thus, seven of 16 of our ischaemic optic neuropathy group had an intraocular pressure exceeding 21 mm Hg during the study period. Raised intraocular pressure may be a predisposing factor in some patients who develop anterior ischaemic optic neuropathy.**

Anterior ischaemic optic neuropathy is a syndrome consisting of sudden loss of peripheral or central vision, or both, associated with optic disc swelling and, commonly, peripapillary nerve fibre layer haemorrhage.[1] Patients experience a sudden loss of vision that may be progressive over days but is stable thereafter. Vision may improve, and recurrences in the same eye are rare.[1] It is associated with a number of vasculitides, including giant cell arteritis and systemic vasculopathies as well as haematological and ocular disease. Most patients with ischaemic optic neuropathy, however, are otherwise healthy or have hypertensive atherosclerotic disease.

Factors which predispose certain eyes to develop ischaemic optic neuropathy have been recognised.[2-4] For example, an eye with a congenitally crowded and small optic disc, with small cup-disc ratio, may be anatomically predisposed. Although the relationship between ischaemic optic neuropathy and elevations of intraocular pressure has been alluded to by several investigators,[5-16] it has not been defined. Foulds identified raised intraocular pressure in 29% of patients with ischaemic optic neuropathy.[6] Raised intraocular pressure has been suggested as contributing to the pathological changes in the optic disc when ischaemic optic neuropathy follows cataract extraction,[14] precipitating an imbalance between the intraocular pressure and the perfusion pressure of the posterior ciliary arteries and, consequently, in the perilaminar capillaries. Despite such observations, contributions of high intraocular pressure to the development of idiopathic ischaemic optic neuropathy have been largely ignored.

In the present study we prospectively evaluated the changes of intraocular pressure throughout the day in patients with non-arteritic ischaemic optic neuropathy and control subjects of similar age and race. The ischaemic optic neuropathy patients were further studied to record their intraocular pressure during routine office visits in the course of their continuing care.

## Material and methods

Sixteen consecutive patients with non-arteritic ischaemic optic neuropathy were prospectively studied from a consultative neuroophthalmology practice (BK). Their age ranged from 54 to 78 years (mean 65·4 years); all were white. Fifteen white subjects age 57 to 74 years (mean 65·0 years) with normal findings on ophthalmic examination served as controls. Anterior ischaemic optic neuropathy was diagnosed in an eye with a relative afferent pupillary defect, dyschromatopsia, an acute decrease in visual acuity, or visual field associated with either sectoral disc oedema or generalised disc oedema with peripapillary haemorrhage. Patients were excluded if they had temporal arteritis, previous ocular surgery, or pain on eye movement. No patient had a family history of glaucoma, or recognised ocular hypertension. No patient was being treated with oral medications known to increase intraocular pressure, or receiving topical medications. No patient had signs of pigmentary dispersion syndrome, angle recession, or pseudoexfoliation.

The intraocular pressure was measured hourly for each group by Goldmann applanation tonometry. The first measurement was at 0800; subsequent measurements continued until 1600. Measurements were performed by ophthalmic assistants and resident physicians who were not aware of the nature of the study. The patients were ambulatory throughout the course of the day. As an adjunct to these hourly measurements the intraocular pressure of the 16 study patients was measured at all subsequent visits to determine whether raised intraocular pressure

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not recognised during the 10-hourly measurements might occur. The range of intraocular pressure was defined as the difference between the highest and the lowest of the hourly measurements.[17] Peak intraocular pressure was defined as the maximum pressure measured during the day.[17] The mean, peak, and range of intraocular pressure for each patient was determined from the 18 observations available (nine hourly measurements for each of two eyes).

Data were analysed by patient (between involved and non-involved eye) and by group. Data were also analysed by direct comparison between cases and controls, the non-involved eyes being used. Data appeared to be approximately normally distributed within each group, though with higher variance in the ischaemic optic neuropathy group. Therefore between-group analysis of means was performed (5% level of significance) by the separate variance formulation of the *t* test.[18] A more conservative statistical approach was employed for the other comparisons where the assumption of a normal distribution was doubtful. Within-subject comparisons were made by the Wilcoxon signed rank test, and between-group comparisons were made by the Mann-Whitney rank sum approach.[18]

## Results

Data were analysed separately for the ischaemic optic neuropathy and control groups (Table I). The mean intraocular pressure for the ischaemic optic neuropathy group was 16·7 mm Hg as compared with a mean intraocular pressure of 15·3 mm Hg for controls (P =0·17). The peak intraocular pressure reached during hourly intraocular pressure determinations for the ischaemic optic neuropathy group and controls is illustrated in Figure 1. The peak intraocular pressure exceeded 21 mm Hg in five of the ischaemic optic neuropathy patients but none of the controls. The mean peak intraocular pressure was 19·9 mm Hg for the ischaemic optic neuropathy group versus 17·6 mm Hg for controls (p =0·034) (Table I). The intraocular pressure exceeded 21 mm Hg during a subsequent visit in two additional patients in whom the hourly determined intraocular pressure peaked at less than 21 mm Hg. Thus, 44% (7/16) of our ischaemic optic neuropathy group had a recorded intraocular pressure exceeding 21 mm Hg during the study period.

The range of intraocular pressure reached during hourly intraocular pressure determinations for the ischaemic optic neuropathy group and controls is illustrated in Figure 2. The range of intraocular pressure was greater for the ischaemic optic neuropathy group (p =0·030). It was 2 to 12 mm Hg, while for the controls it was 2 to 6 mm Hg. Eight of 16 ischaemic optic neuropathy patients had a range of intraocular pressures of 6 mm Hg or more as compared with only three of 15 controls.

There were no statistically significant differences within each group for right eye-left eye comparisons of standard deviations of mean, peak, or range of intraocular pressure (Table II). Within the ischaemic optic neuropathy group there were no statistically significant differences of peak, mean, or range of intraocular pressure when the involved eye was compared with the non-involved eye.

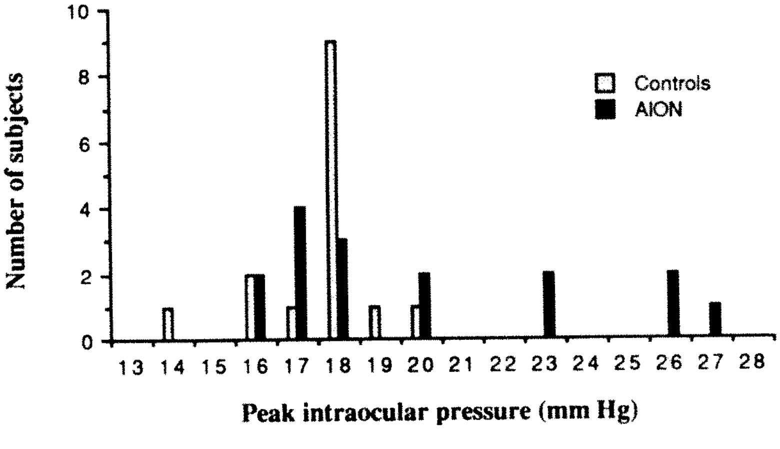
There was, however, a trend for more variation of intraocular pressure in the involved eye than the non-involved eye (p=0·056). Moreover, there were significant differences in standard deviations for the ischaemic optic neuropathy involved eye versus control eye (OD and OS) standard deviation (p=0·024 and 0·0096 respectively). A direct comparison of the variation in hourly values of intraocular pressure for the ischaemic optic neuropathy non-involved eye was intermediate between the ischaemic optic neuropathy involved eyes and either control eye (p=0·075 and 0·093 respectively).

TABLE I *Intraocular pressure* in ischaemic optic neuropathy and controls (mm Hg)*

| | *Ischaemic optic neuropathy* | *Controls* | *p Value* |
|---|---|---|---|
| Mean | 16·7 (3·5) | 15·3 (1·8) | 0·17 |
| Peak | 19·9 (3·8) | 17·6 (1·4) | 0·034 |
| Range | 5·9 (2·3) | 4·5 (1·1) | 0·030 |

* Mean (standard deviation).

*Figure 1: Frequency histogram of the peak intraocular pressure during hourly determinations of intraocular pressure in ischaemic optic neuropathy and control population.*



## Discussion

The cause of non-arteritic anterior ischaemic optic neuropathy has not been established with certainty.[1] Histological studies in human eyes support the concept of the posterior ciliary circulation as the vascular bed involved in its pathogenesis.[19-21] The anatomical sites of ischaemic injury in ischaemic optic neuropathy are the prelaminar, laminar and immediate postlaminar region of the optic nerve. The prelaminar and laminar portions of the optic nerve are supplied primarily by the posterior ciliary arteries. These vessels supply the distal nerve both directly and to some extent indirectly through the peripapillary choroidal arteries.[22] The retrolaminar optic nerve is supplied predominantly by the pial plexus, which receives contributions from the posterior ciliary arteries, extraneural branches of the central retinal artery, and small penetrating branches from numerous orbital arteries. This particular neurovascular anatomy may render these regions especially vulnerable to ischaemic insult and infarction.[23] It has been described as representing a watershed

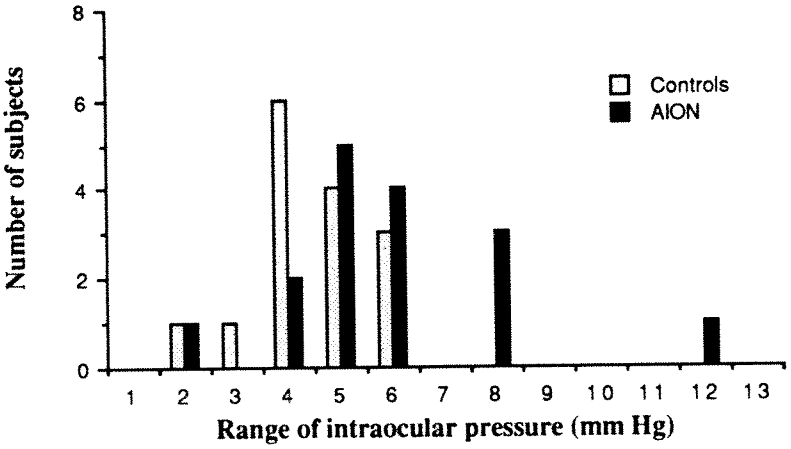


*Figure 2: Frequency histogram of the range of intraocular pressure during hourly determinations of intraocular pressure in ischaemic optic neuropathy and control population.*

TABLE II *Descriptive statistics for within-subject standard deviation of nine consecutive hourly determinations of intraocular pressure*

| | *Anterior ischaemic optic neuropathy* | | | | *Control* | |
|---|---|---|---|---|---|---|
| | *Involved Eye* | *Non-Involved Eye* | *Eye* | | *Eye* | |
| | | | *OD* | *OS* | *OD* | *OS* |
| Mean | 1·68 | 1·46 | 1·57 | 1·58 | 1·26 | 1·18 |
| Median | 1·67 | 1·47 | 1·63 | 1·56 | 1·23 | 1·13 |
| SD | 0·60 | 0·49 | 0·48 | 0·62 | 0·43 | 0·35 |
| Max | 3·12 | 2·35 | 2·36 | 3·11 | 2·50 | 1·73 |
| Min | 0·78 | 0·42 | 0·42 | 0·79 | 0·69 | 0·64 |

zone between the retinal and choroidal circulations.[24] These regions might therefore be especially susceptible to impaired perfusion states, particularly since the choroidal circulation does not have autoregulatory capabilities (as demonstrated in the cat).[25] The laminar vessels are unique in being contained within a connective tissue septum,[26] which may also make them more vulnerable to senile fibrotic changes. Changes have been demonstrated histologically in the posterior ciliary arteries of man in association with atherosclerotic and arteriosclerotic disease.[30] Furthermore, the laminar and prelaminar vessels are subjected to an especially high extramural pressure owing to the level of intraocular pressure.[24] Any imbalance produced either by lowering of the perfusion pressure or increase of the intraocular pressure could lead to local ischaemia as the result of compromised blood flow.[14]

All factors concerned with perfusion pressure have prognostic and pathophysiological import as regards the functional integrity of the anterior optic nerve. The deleterious influence of low blood pressure,[27 28] severe haemodynamic crisis,[29] and systemic vascular disease,[30] and the favourable influence of higher levels of blood pressure, [27 28] have been documented. The anatomical predilection of small, crowded optic nerves, with small cup-disc ratios, to the generation of ischaemic optic neuropathy has been recognised.[2-4]

Raised intraocular pressure may be another factor in some patients. A raised intraocular tension may precipitate enough of a drop in perfusion pressure in the posterior ciliary bed to be haemodynamically significant in the anatomically susceptible patient. The decreased perfusion pressure in the posterior ciliary arteries could lead to ischaemic damage at the level of the laminar and immediately retrolaminar portions of the optic nerve. Such changes have been shown experimentally.[31] There appears to be preferential involvement of or susceptibility to decreased perfusion in the vessels of the prelaminar region of the optic nerve so that these vessels may suffer ischaemic insult early.[32] Blumenthal *et al* have demonstrated that flow ceases in the choroidal circulation of man at intraocular pressures significantly lower than levels required to produce decreased flow within the retinal vascular tree.[32] They inferred that the peripapillary choroidal vessels and optic disc vessels were the most vulnerable portion of the choroidal circulation to increases in intraocular pressure.[32] The compact arrangement of neural and vascular elements within an anatomically susceptible scleral canal makes the process of infarction, with resultant oedema, lead to more infarction and oedema. Perfusion in this zone would become especially precarious with higher intraocular pressures.

Our study suggests that high intraocular pressure may be a factor in some patients who develop idiopathic ischaemic optic neuropathy. The peak and the range of variation of the hourly intraocular pressure was greater in the ischaemic optic neuropathy group than in controls. The increased range of variation of intraocular pressure seen in our ischaemic optic neuropathy group is consistent with previous reports which show that the range of intraocular pressure is wider in patients with higher levels of intraocular pressure.[33-41] Seven of 16 of our patients (44%) had an intraocular pressure above 21 mm Hg. These determinations were recorded between 0800 and 1600 and may not accurately demonstrate the extent of diurnal fluctuation of intraocular pressure. Nevertheless almost half of our ischaemic optic neuropathy group had a raised intraocular pressure – more than seen in our control group or expected from epidemiological population surveys.[42 43] Though the number of patients studied was small, our findings suggest that high intraocular pressure could be an additional predisposing factor if not an initiating event in the development of non-arteritic anterior ischaemic optic neuropathy in some cases. An alternative interpretation would suggest that the ischaemic event at the nerve head results in ocular hypertension. Our study was not designed to differentiate these two possibilities.

If high intraocular pressure is associated with the occurrence of anterior ischaemic optic neuropathy in some patients, perhaps treatment to lower intraocular pressure might afford some protection for the non-involved eye by improving perfusion pressure in the vessels of that optic nerve head. Such a theoretical basis for intervention has been suggested previously.[44] It is entirely analogous to the logic behind the institution of steroid therapy in the arteritic variety of ischaemic optic neuropathy, namely, to protect the uninvolved eye. With the availability of relatively selective β-1 adrenergic blocking agents, which may lower intraocular pressure without constricting peripheral vascular beds or placing the microvasculature at further risk for vasoconstriction,[45 46] such a therapeutic trial seems worth considering.

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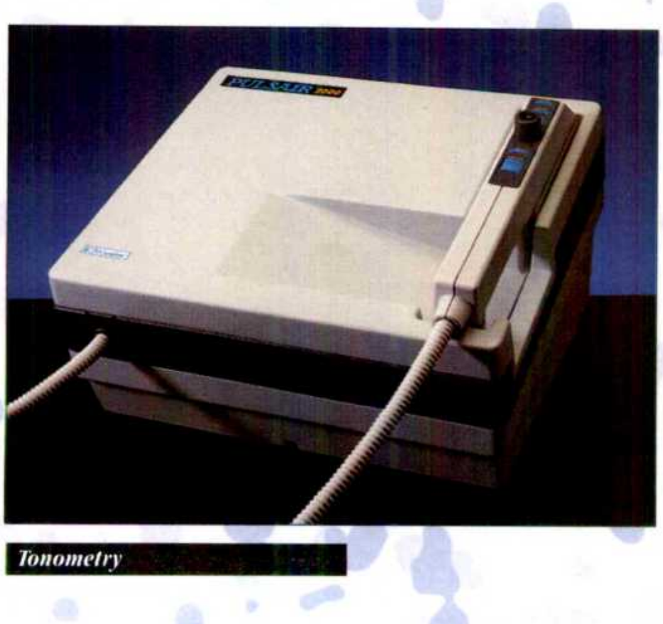

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# Cyclocryotherapy: a review of cases over a 10-year period

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## Abstract

**There are conflicting reports on the value of cyclocryotherapy in the management of glaucoma. This retrospective study was carried out to assess the efficacy and complication rate of this procedure. The case notes of all patients undergoing cyclocryotherapy at a single centre over a 10-year period were reviewed. Case records were available for 68 eyes of 64 people. Thirty-eight eyes had neovascular glaucoma, nine had aphakic glaucoma, nine had angle closure glaucoma, three had primary open angle glaucoma, and nine had secondary open angle glaucoma. The mean follow-up periods for these groups varied from 2·0–6·3 years. The mean reduction in intraocular pressure following treatment varied from 7·9 mm Hg in the secondary open angle glaucoma group to 24·3 mm Hg in those with angle closure glaucoma. Pressure was controlled in 29·4% overall, ranging from 66·7% in the angle closure and primary open angle groups to 0% in the secondary open angle group. Of the painful eyes 71% were rendered comfortable, indicating that pain relief from cyclocryotherapy is not due solely to pressure control. 30% of the patients lost their vision following the procedure, phthisis occurred in 11·8% and four eyes (5·9%) went on to enucleation. Our results indicate that cyclocryotherapy affords good pain relief, without good pressure control, in various types of glaucoma. While there is an apparent high complication rate, visual loss and phthisis cannot be ascribed directly to the procedure, since these are eyes with a poor prognosis.**

Since its description by Bietti in 1950[1] cyclocryotherapy has retained a place in the management of certain types of glaucoma. It is non-invasive and relatively easy to perform, but there are conflicting reports of its efficacy, and some series show a high incidence of visual loss and progression to phthisis in treated eyes. It was therefore decided to carry out a retrospective review of all cases undergoing cyclocryotherapy at our unit over the past 10 years to assess the efficacy and complication rate of this procedure.

## Materials and methods

Included in this study are all available case notes of patients undergoing cyclocryotherapy over a 10-year period up to April 1989. Case records were available from 68 eyes of 64 people. The mean age for all patients was 67 years, range 13–88 years.

A carbon dioxide cryosurgical unit and a 2·5 mm probe were used for all procedures. A full description of the operation was not available for all cases, but where indicated typical parameters were a 60-second single freeze, in 6–8 applications, covering 180° of the ciliary body.

The patients received topical atropine and corticosteroids postoperatively, and in addition glaucoma medication was continued as necessary.

## Results

For the purposes of analysis the cases were categorised as shown in Table 1. Thirty-eight eyes had neovascular glaucoma, of which 26 were due to a central retinal vein occlusion and seven to diabetes. Nine eyes had aphakic glaucoma, nine had angle closure glaucoma, three had primary open angle glaucoma, and nine had secondary open angle glaucoma. The mean follow-up periods for these groups varied from 2·0 to 6·3 years (Table 2). The aim of treatment in all groups was reduction in intraocular pressure and/or control of pain. This latter consideration applied particularly to the neovascular group, 87% of whom had pain preoperatively.

The mean reduction in intraocular pressure following treatment varied from 7·9 mm Hg in the group with secondary open angle glaucoma to 24·3 mm Hg in those with angle closure (Table 3).

An intraocular pressure of more than 0 mm Hg but less than 22 mm Hg at one month was taken to indicate control of intraocular pressure. By this criterion the pressure was controlled in 29·4% of eyes overall, ranging from 66·7% in the angle closure and primary open angle groups to 0% in the secondary open angle group.

Of those eyes which were painful preoperatively 71·4% were comfortable following the procedure.

The figures for visual acuity changes must be interpreted with caution, since the case notes indicated that of the two patients in the primary open angle glaucoma group who lost vision one had age related macular changes and the other had anterior ischaemic optic neuropathy. If these two cases are ignored, then 30·3% of patients lost vision following the procedure.

Phthisis was defined as an intraocular pressure of 0 mm Hg or a shrunken eye, and this occurred in 11·8% of cases overall.

TABLE I *Distribution of glaucoma categories in this series. SD = standard deviation*

| *Category* | *Number* | *Mean age* | *SD* |
|---|---|---|---|
| Neovascular glaucoma | 38 | 67 | 16·9 |
| Aphakic glaucoma | 9 | 72 | 13·5 |
| Angle closure glaucoma | 9 | 75 | 10·8 |
| Primary open angle glaucoma | 3 | 75 | 9·2 |
| Secondary open angle glaucoma | 9 | 51 | 27·6 |

TABLE 2 *Preoperative data and follow-up periods*

| | *Neovascular glaucoma* | *Aphakic glaucoma* | *Angle closure glaucoma* | *POA glaucoma* | *Secondary glaucoma* |
|---|---|---|---|---|---|
| IOP | | | | | |
| Mean | 54·8 | 39·5 | 46·4 | 27·3 | 39·6 |
| SD | 12·4 | 14·1 | 11·2 | 4·6 | 9·4 |
| Acuity | | | | | |
| 6/12+ | 0 | 1 | 0 | 3 | 0 |
| 6/18–6/60 | 0 | 0 | 1 | 0 | 1 |
| CF | 4 | 3 | 2 | 0 | 1 |
| HM | 9 | 3 | 2 | 0 | 4 |
| PL | 6 | 1 | 0 | 0 | 0 |
| NPL | 19 | 1 | 4 | 0 | 3 |
| Pain | 33 | 6 | 4 | 0 | 6 |
| Follow up: | | | | | |
| Mean (years) | 2·83 | 2·44 | 1·98 | 6·33 | 2·31 |
| Range | 0·08–9 | 1·5–5 | 0·02–10 | 5–8 | 0·02–8 |

CF = count fingers. HM = hand movements. PL = perception of light. NPL = no perception of light. POA glaucoma = primary open angle glaucoma. IOP = intraocular pressure.

TABLE 3 *Postoperative data*

| | *Neovascular glaucoma* | *Aphakic glaucoma* | *Angle closure glaucoma* | *POA glaucoma* | *Secondary glaucoma* |
|---|---|---|---|---|---|
| Mean IOP reduction* (mm Hg) | 20·4<br>(17·8) | 11·8<br>(12·8) | 24·3<br>(22·0) | 8·0<br>(3·6) | 7·9<br>(8·3) |
| IOP† ≤21 mm Hg | 10<br>26·3% | 2<br>22·2% | 6<br>66·7% | 2<br>66·7% | 0 |
| Comfortable | 24/33<br>72·7% | 5/6<br>83·3% | 3/4<br>75% | – | 3/6<br>50% |
| Vision: | | | | | |
| Worse | 13 | 2 | 3 | 2 | 2 |
| Same | 25 | 6 | 6 | 1 | 6 |
| Improved | 0 | 1 | 0 | 0 | 1 |
| Repeat treatment | 4 | 1 | 3 | 0 | 2 |
| Phthisis | 6 | 1 | 1 | 0 | 0 |
| Enucletion | 2 | 0 | 1 | 0 | 1 |

†At 1 month.
*SD in parentheses.

TABLE 4 *Area of ciliary body treated in eyes which subsequently became phthisical*

| | *Area of ciliary body treated* | | | |
|---|---|---|---|---|
| | *180°* | *270°* | *360°* | *Unknown* |
| Neovascular glaucoma | 1 | 2 | 2 | 1 |
| Angle closure glaucoma | 0 | 0 | 1 | 0 |
| Aphakic glaucoma | 0 | 0 | 1 | 0 |

Four eyes (5·9%) went on to have enucleation.

The only recorded early complication recorded was a hypopyon on the first postoperative day in one patient with aphakic glaucoma. This settled satisfactorily with topical corticosteroids.

## Discussion

In our series neovascular glaucoma forms the largest group, comprising 56% of cases. This group accounted for 51% of cases reported by Brindley and Shields[2] and only 21% of the series reported by Caprioli *et al.*[3] The difference may reflect the fact that these reports are from specialist glaucoma centres.

The intraocular pressure at one month after operation, or as soon as possible after that, was chosen because the full effect of the procedure should be evident by this time.[4] Although there was a significant reduction in intraocular pressure in all groups, particularly in neovascular and angle/closure glaucoma, pressure control at one month was disappointing, with only 29·4% of eyes controlled overall and only 26·3% controlled in the neovascular group. This is lower than other published series, which report conrol in 55–66% of neovascular glaucoma[2,3,5,6] and 59–67% overall.[2,3,7] Our results may reflect inadequate technique, since the procedure is performed infrequently, as shown by the record of only 68 such operations over a 10-year period, and experience in the technique is therefore limited. The variation in technique recorded in the case notes supports this notion.

Cyclyocryotherapy decreases aqueous production by damaging the ciliary epithelium and the vascular supply to the ciliary body. The destructive effect depends on the freezing rate and the tissue temperature achieved. At −15°C extracellular water crystallises, leading to increased extracellular concentration of electrolytes, with resulting cellular dehydration and disruption. Below −15°C intracellular ice crystals form, causing far greater damage.[4]

To ensure placement over the pars plicata a 2·5 mm probe should be used, and this should be placed 1 mm from the limbus nasally, temporally, and inferiorly, and 1·5 mm superiorly.[4,8] A freeze temperature of −80°C is desirable to produce a toxic concentration of electrolytes.[4] The freeze time should be longer than 30 seconds so that the changes occurring in cells can cause permanent damage. At −80°C a 60-second application appears to be most appropriate.[3] There is a direct relationship between the extent of treatment and intraocular pressure reduction, and this parallels the histological changes resulting from treatment.[9] Most of the serious complications (hypotony, phthisis bulbi) are found after 360° treatment.[3] The initial treatment should therefore be limited to one hemisphere.

Despite poor pressure control in our series, the procedure rendered 71·4% of painful eyes comfortable. This indicates that pain relief from cyclocryotherapy is not due solely to pressure control.

The visual loss from other causes in two of the patients with open angle glaucoma indicates that caution must be exercised when attributing decrease in visual acuity to the cyclocryotherapy. It must be borne in mind that the majority of these patients are elderly (mean 67 years) and that these are unhealthy eyes, many of which have a poor prognosis regardless of treatment. Our rate of visual loss of 30% overall and 34% in neovascular glaucoma is relatively low. Brindley and Shields[2] report a 60% visual loss overall and 68% in the neovascular group. Other published figures for visual loss in the latter group are 70%[3] and loss of light perception in 37–59%.[5,6] If the two patients with primary open angle glaucoma who lost vision are excluded, then of our patients who lost vision only two out of 20 achieved control of intraocular pressure. It may be therefore, that it is failure to lower the intraocular pressure which is responsible for visual loss rather than the procedure itself.

Our figure of 11·8% progression to phthisis

(15·8% in the neovascular group) accords with other series. Caprioli *et al*[3] reported phthisis in 12% with 360° treatment and in 6% with 180° treatment. Brindley and Shields[2] found 12% overall and 22% in the neovascular group. Krupin and Mitchell[6] noted phthisis in 14% of neovascular cases at 12 months, and in 34% ultimately, with mean follow-up of 24·9 months and phthisis developing at a mean of 14·4 months. Although our figures were too small for statistical analysis, it was noted that of the seven patients with phthisis for whom operative details were recorded the extent of treatment was 360° in four, 270° degrees in two, and 180° in only one (Table 4). Overall, the extent of treatment was 180° in 35, 270° in 11, 360° in 13, and unknown in nine. This lends support to the notion that no more than 180° should be treated at a single session.

Our results indicate that cyclocryotherapy affords good pain relief, without good pressure control, in various types of glaucoma. While there is an apparent high complication rate, visual loss and phthisis cannot be ascribed directly to the procedure, since these are eyes with a poor prognosis. It should be borne in mind that prevention of rubeotic glaucoma is paramount, and that there are very favourable reports for the use of photocoagulation combined with modified filtration surgery for neovascular glaucoma.[10 11]

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# Macular recovery function (nyctometry) in diabetics without and with early retinopathy

E Midena, T Segato, M Giuliano, M Zucchetto

**Abstract**

**Nyctometry was used to assess macular recovery function in 234 diabetic patients; their retinopathy ranged from no retinopathy (99) to early background retinopathy (135). None had visual symptoms or macular oedema. Abnormal (reduced) nyctometry findings were significantly and directly related to the deterioration of diabetic retinopathy. There was no significant association between reduced or normal nyctometry findings and glycaemia at the time of the examination. The value of nyctometry in screening and follow-up is discussed.**

Diabetic retinopathy is considered to be a disease affecting either retinal blood vessels or neurosensory retina.[1] The neurosensory alterations are caused in part by vascular alterations, but they also, and perhaps primarily, reflect the local and systemic metabolic derangements due to diabetes. The retinal neurosensory losses may predict the evolution of retinopathy toward more advanced forms[2-4] and sometimes may precede the onset of clinically detectable retinopathy.[5-7] Such tests therefore seem to be useful not only for predicting the evolution of established diabetic retinopathy, but also for monitoring the retinal state of diabetic patients, when better control or new drugs are given to prevent the appearance of clinical retinopathy. The neurosensory losses involve macular recovery function among others.

The present study was undertaken to examine in more detail the relationship between modifications of macular recovery function, evaluated by means of nyctometry, and the retinal situation in diabetics without or with early diabetic retinopathy.

## Patients and methods

The patients consisted of 234 diabetics seen at the Retinal Vascular Clinic, Institute of Ophthalmology, the University of Padova. The mean duration of diabetes was 13 years (SD 7). All patients had a visual acuity of 1·0 (equivalent to 6/6). Their retinopathy ranged from no retinopathy (99 subjects) to early background retinopathy. The retina was examined by direct and indirect ophthalmoscopy and fundus biomicroscopy. Fluorescein angiography was performed in diabetics clinically classified without retinopathy; it was negative in all these subjects. The patients with retinopathy were divided into two groups: I, with some microaneurysms and some retinal haemorrhages, but total haemorrhages less than standard photograph 2A of the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (83 subjects); II, with group I lesions and some hard exudates, less than standard photograph 3 of the ETDRS protocol, all located outside the macular zone (52 patients).[8] No patient had soft exudates, intraretinal microvascular abnormalities, or signs of macular oedema, nor had any patient previously received photocoagulation. No cardiovascular, neurological, or other ocular disease was present at the time of the examination. Among these diabetics 134 randomly selected subjects underwent blood sugar determination (Reflocheck, Boehringer, Mannheim, FRG) immediately after the macular recovery function had been studied.

### NYCTOMETRY

Nyctometry is a dynamic measure of the initial 2-minute course of macular recovery function following preadaptation to a strong uniform illumination of a large area of the retina. The instrument we use is the Registriert Nyktometer (Carl Zeiss, Jena, DDR) which allows a minimal intervention by the examinator. Nyctometry was performed on both eyes; the recording on a single eye took 6·5 minutes.

The patient looks into a white coloured globe, in which a sight test chart is placed opposite to the patient's eye. The test chart is composed of 10 lines (visual acuity from 0·1 to 1·0) of numbers, which can be modified to prevent memorisation. The optical system of the instrument is made to determine long distance visual acuity.

Briefly, nyctometry consists of three steps. The first is a 3-minute adaptation to strong light (7000 asb; 2200 cd/m$^2$). The light is then switched off and the 2-minute initial phase of dark adaptation begins. During this phase the patient has to read the test signs (illumination 0·5 asb; 0·16 cd/m$^2$); thus we record the increase in visual acuity as a function of time. The last step is a measure of patient's sensitivity to glare (for details of technique see Frost-Larsen *et al*[9]). The last two phases are graphically recorded on a form. The individual graphic is compared with standard age-related ranges of normality (20–30, 31–50, 51–60, 61–70 years). The result is reported as reduced or normal. Reduced nyctometry means a value below the 2·5 percentile of the normal age-related range.

The statistical analysis was by the $\chi^2$ test. When the results in the two eyes were similar, data from the right eye are reported. In addition the results of nyctometry were quantified by the summation method proposed by Frost-Larsen and Larsen.[4] This method, called by the proposers 'intensified calculation of macular recovery time', gives an absolute number for

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TABLE I *Nyctometry determinations compared with retinal state of diabetic patients*

| | | *Retinopathy* | | |
|---|---|---|---|---|
| *Nyctometry* | *No retinopathy* | *I* | *II* | *Total* |
| Reduced | 37 (37·4%) | 38 (45·8%) | 35 (67·3%) | 110 |
| Normal | 62 (62·6%) | 45 (54·2%) | 17 (32·7%) | 124 |
| Total | 99 | 83 | 52 | 234 |

p=0·002.

each examination. This number results from the sum of the products of ten times each reached step of visual acuity (0·1=1, 0·2=2 . . .) and the difference between 120 seconds (the whole 2-minute course of cone adaptation) and the actual time (in seconds) taken to reach that step.

## Results

In a preliminary phase we performed nyctometry in a large population of normal subjects of different ages (20 to 70 years). Their macular recovery function always lay in the normal age related range given by the manufacturer of the instrument (Midena *et al*, unpublished data).

Table I summarises the results of nyctometry evaluation in our diabetic population. The proportion of abnormal (reduced) results increased with deterioration of the retinopathy: 45·8% in group I, 67·3% in group II. Moreover we observe that 37·4% of the patients classified (clinically and angiographically) without retinopathy showed altered macular recovery function. The nyctometry results were significantly related ($\chi^2$=12·34, df=2, p=0·002) to the progression of subclinical and clinical diabetic retinopathy.

The blood glucose level at the time of nyctometry determination did not influence the result of the examination (Table II). The quantitative data of nyctometry (Table III) showed a decrease of this function with age in normal and diabetic subjects.

Moreover it showed in each age group a worsening of macular recovery function with deterioration of the retinopathy.

## Discussion

Nyctometry is a standardised technique used to measure macular recovery function in a short time. The test lasts 6·5 minutes only. The result is easily compared with standard age related curves. The normal data from our laboratory appeared to be identical to those given by the manufacturer; we therefore use the age ranges provided by the manufacturer. In consequence the result is independent of the patient's age. This is a great advantage in respect of other functional methods, where normative age related data are not available. Some authors consider nyctometry to be a technique for measuring dark adaptation – more precisely, the dark adaptation of the cone system.[10] Nyctometry quantifies not only the dark adaptation of the cone system but also the macular sensitivity to glare. We therefore think it is entirely adequate for studying the function of the macula.

TABLE II *Blood glucose level at the time of nyctometry examination in 134 randomly selected diabetics*

| | *Glycaemia (mmol/l)* | | | | |
|---|---|---|---|---|---|
| *Nyctometry* | *6·7* | *6·8–8·9* | *9·0–11·0* | *>11·0* | *Total* |
| Reduced | 11 (33·3%) | 18 (50·0%) | 20 (58·8%) | 20 (64·5%) | 69 |
| Normal | 22 (66·7%) | 18 (50·0%) | 14 (41·2%) | 11 (35·5%) | 65 |
| Total | 33 | 36 | 34 | 31 | 134 |

p=0·065.

TABLE III *Nyctometry quantified by the summation method (Frost-Larsen and Larsen[4]). In normal and diabetic subjects the absolute value of nyctometry has been calculated by the summation method (see text) and the mean of each age group is reported (standard deviation in brackets)*

| | | *Diabetics* | | |
|---|---|---|---|---|
| *Age group* | *Normals* | *No retinopathy* | *Retinopathy I* | *Retinopathy II* |
| 10–30 yr | 712·5 (306·8) | 570·2 (446·7) | 502·0 (349·3) | 139·3 (102·3) |
| 31–50 yr | 697·0 (217·8) | 538·2 (359·0) | 305·1 (180·3) | 348·6 (264·8) |
| 51–60 yr | 499·2 (200·8) | 388·2 (301·2) | 389·0 (308·0) | 197·5 (171·7) |
| 61–70 yr | 262·3 (123·9) | 332·3 (151·3) | 248·1 (156·5) | 206·3 (181·5) |

Previous reports on nyctometry have suggested that it can be used to predict the progression of background retinopathy to the proliferative form.[2 4 9] Similar results have been reported with the electroretinogram oscillatory potentials.[2 3]

In contrast very few reports have dealt with the use of nyctometry in diabetics without or with early retinopathy. Gliem and Schultze[11] showed that 42 of 159 eyes of diabetics without retinopathy gave abnormal nyctometry results. But their study suffers from some methodological inaccuracies: they did not use age related normal ranges; the results of nyctometry were related to nyctometry without considering the age of the patient. Frost-Larsen and Larsen[4] reported that two out of 57 eyes of diabetics without retinopathy gave reduced nyctometry results, but their paper does not consider this problem in detail.

Our data clearly show, in a well defined series of patients, that reduced nyctometry is directly and strongly related to the progression of retinal (functional and anatomical) derangements due to diabetes. This is confirmed by a quantitative method. The limit of this and the other methods proposed to quantify nyctometry is the inadequacy of each to describe adequately the curve obtained with this test. The final visual acuity and the Frost-Larsen and Larsen summation method show too great a variation in results.[4 11] The area under the curve – proposed by Brinchmann-Hansen *et al*[12] – gives equal results with different curves.

We therefore consider that so far the best way to classify nyctometry results is qualitatively (normal, reduced). Our data are similar to those obtained by means of other functional tests.[3 5 13–15]

Moreover the results of nyctometry are independent of the glycaemic status of a patient who is healthy at the time of the investigation. No comparable data are available from previous studies performed with other functional tests in diabetics. We have also shown that 37·4% of subjects considered by current standards to be unaffected by retinopathy give reduced nyctometry results, an indication of abnormal macular function. At present we do not know why macular recovery function is abnormal in these subjects. They may perhaps represent, among diabetics without retinopathy, a group in whom retinopathy will soon appear. A similar hypothesis has been proposed by Della Sala *et al*[13] using a contrast sensitivity test. To confirm (or not) this hypothesis a five-year prospective study is in progress.

Our data also suggest that nyctometry might be used as a simple, quick, and non-invasive test to monitor the function of the macula in diabetics during intensified metabolic control or drug treatment. A further implication of our results on nyctometry in diabetic patients should also be pointed out. The site of the initial phase of dark adaptation is not yet completely defined, but it is thought to involve neural processes in the retina.[16-18] Nyctometry is thus a test which provides information about the function of a specific part not only of the visual system but also of the retina. This could provide new insight into the pathophysiology of diabetic retinopathy.

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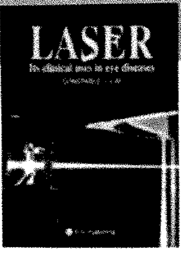

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# A trial of surgery for trichiasis of the upper lid from trachoma

M H Reacher, M J E Huber, R Canagaratnam, A Alghassany

**Abstract**

**Three surgeons operated on upper eye lids of northern Omani villagers for trichiasis due to trachoma using a standardised protocol. The lids were graded as minor trichiasis, five or fewer lashes; major trichiasis, six or more lashes; and lid closure defect. Operative success was defined as no lash/eyeball contact and complete gentle lid closure. One hundred and sixty five lids with major trichiasis were allocated by random number tables to one of five operations: bilamellar tarsal rotation (Ballen), tarsal advance and rotation (modified Trabut), eversion splinting (grey line), tarsal advance (lid split), and tarsal grooving (Streatfield-Snellen) operations. Bilamellar tarsal rotation was significantly more successful than eversion splinting ($\chi^2=7{\cdot}0$, $p<0{\cdot}01$); tarsal advance ($\chi^2=12{\cdot}4$, $p<0{\cdot}001$), and tarsal grooving ($\chi^2=23{\cdot}7$, $p<0{\cdot}001$), but not significantly more successful than tarsal advance and rotation ($\chi^2=2{\cdot}9$, $p>0{\cdot}05$). Two of 32 (6%) lids with lid closure defect were successfully treated with tarsal advance; trichiasis was relieved in nine and lid closure defect in 10. It is suggested that bilamellar tarsal rotation and tarsal advance and rotation are effective operations for major trichiasis, but tarsal advance is ineffective where trichiasis and lid closure defect coexist.**

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The provision of community based lid surgery to correct trichiasis and lid closure defects is a key strategy for prevention of trachomatous blindness.[1,2] However, reports of the effectiveness of standard operations for upper lid trichiasis are few and limited in applicability to individuals from trachoma endemic communities, because most cases have causes other than trachoma[3,4] or losses to follow-up were large.[5] In order to identify effective operations for upper lid trichiasis from trachoma in rural northern Oman, where a high prevalence of potentially blinding lid deformities exist,[6] a trial of standard operations was undertaken for patients brought for surgery by staff of the Oman Prevention of Blindness Programme. The programme comprises six teams of primary eye care workers. They visit villages and towns regularly, where mapping and home visits are performed prior to the preparation of a community census. Team activities include screening for inflammatory trachoma and trichiasis and compiling a list of individuals in need of lid surgery. The patients are examined at a central location, and the census list is used to ensure complete coverage. Surgery is subsequently performed at local hospitals or health centres equipped for eye lid surgery. Patients meeting our criterion of major trichiasis were commonly seen and underwent one of five operations representative of a principal type of upper lid entropion surgery. Lids with defective lid closure were less commonly seen and underwent tarsal advance.

*Figure 1: Five operations of the upper lid for trichiasis from trachoma.*

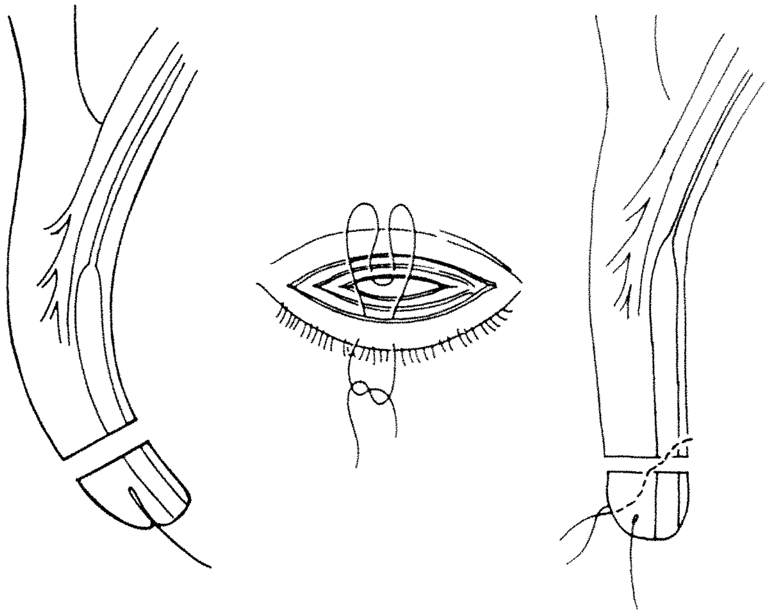

*Figure 1A: Bilamellar tarsal rotation.*

## Patients and methods

Adults diagnosed as having trichiasis by primary eye health workers and who wanted treatment were brought for eye lid surgery. Before operation a history of previous upper lid operations was obtained and an ophthalmologist examined the patient with 2·5× loupes with eyes in the primary position, in up-gaze to view the lid margin, and closed gently as in sleep to evaluate lid closure. Upper lids were graded in the primary position as follows:

*Minor trichiasis:* Lid closure complete; one to five lashes in contact with eye ball.

*Major trichiasis:* Lid closure complete; six or more eye lashes in contact with eye ball.

*Defective closure:* Lid closure incomplete; any number of lashes in contact with eye ball.

The extent of trichiasis, from less than half or more than or equal to half the lid width, was also recorded. Informed consent for lid surgery was obtained. Pregnant women were excluded owing to a cultural aversion to surgery in pregnancy. Details of patients were recorded on a proforma. The operations studied were in routine use and the trial was approved by the Ministry of Health of Oman. Upper lids with major trichiasis underwent one of the following operations allocated by random number tables: bilamellar tarsal rotation[7]; tarsal advance and rotation[8];

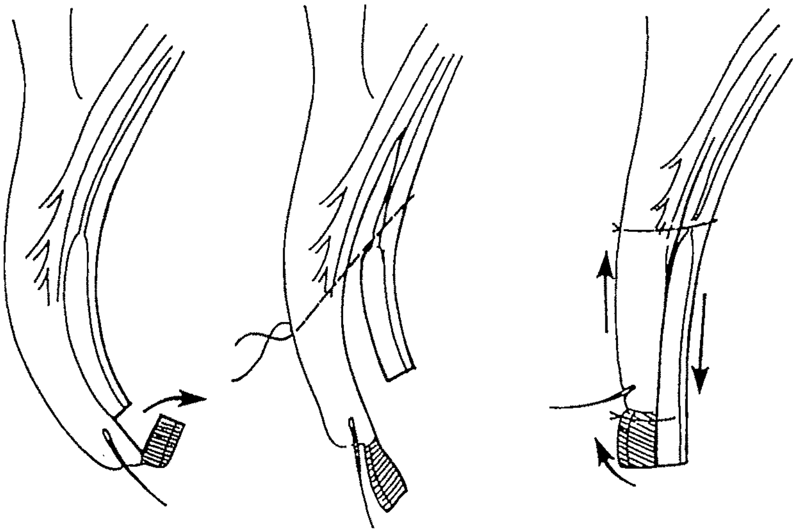

*Figure 1B: Tarsal advance and rotation.*

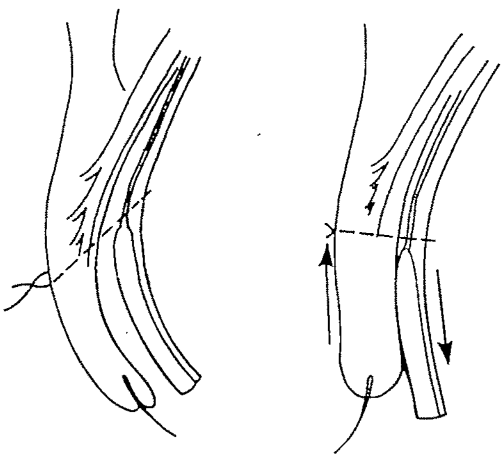

*Figure 1D: Tarsal advance.*

eversion splinting[5]; tarsal advance[8]; and tarsal grooving[9] (Figs 1A-E). Lids with defective closure underwent tarsal advance.[8]

Surgery was performed with standard aseptic technique by one of three surgeons according to a standardised protocol under local anaesthesia with topical 4% and up to 3 ml of 2% lignocaine with 1: 200 000 adrenaline infiltrated into the neuromuscular plane. Sofratulle gauze and 5–0 silk were used for eversion splinting and 4–0 chromic catgut for the other operations. After operation the eyes were dressed with tetracycline 1% ointment instilled into the lower fornix and a pad.

Postoperative examination and dressings with further application of tetracycline 1% eye ointment were performed by ophthalmologists and by ophthalmic trained nurses either at the clinic or at the patient's home for six days. On the sixth day dressings were removed, and tetracycline 1% ointment was given to be applied twice daily to both eyes for six weeks to terminate active ocular chlamydia infection.[1] All patients were examined again by ophthalmic nurses 14 days postoperatively for eye lash/eye ball contact, and silk sutures and gauze rolls were removed from lids that had undergone eversion splinting.

The primary measure of outcome was treatment success. This was defined as no eye lash/eye ball contact in the primary position of gaze and complete eye lid closure on asking the patient to close the eyes gently as in sleep.

Follow-up examination of all patients was performed with a 4× halogen illuminated loupe (Keeler) by MR either at clinics or at the patient's home. Information from proformas was entered into dBaseIII plus (Ashton-Tate) for analysis on microcomputer. The proportions of successful outcome at follow-up were compared by allocated operation and by operation done. Those lost to follow-up were included in the denominator. Crossovers of treatment after allocation occurred in five lids as follows. Three lids allocated to tarsal grooving were converted to bilamellar tarsal rotation, as there was insufficient tarsus for grooving: all had undergone previous surgery. One patient allocated tarsal advance became agitated at surgery, and eversion splinting was performed instead. One lid allocated to tarsal advance and rotation underwent tarsal advance in error. Eye lash/eye ball contact was present at 14 days postoperatively in one patient who had undergone eversion splinting, but in no others.

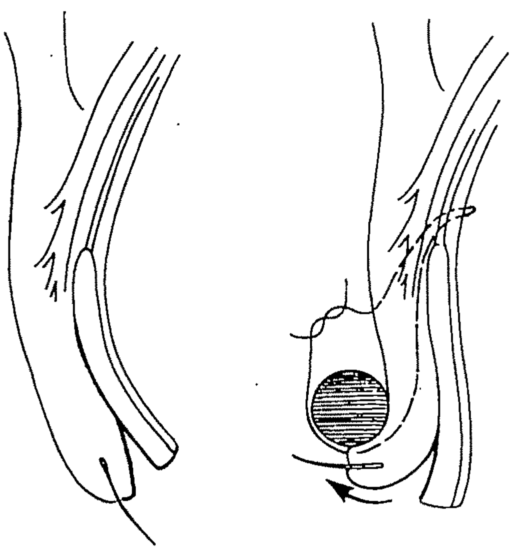

*Figure 1C: Eversion splinting.*

**Results**

One hundred and sixty five patients with major trichiasis and 32 with defective lid closure were enrolled consecutively between 1 January and 2 July 1986. A significant association between a history of previous surgery and defective lid closure was noted (Table I). The 165 lids with major trichiasis were allocated to one of five operations. Tarsal grooving had a smaller proportion of lids that had undergone previous surgery. Bilamellar tarsal rotation and tarsal grooving had a higher proportion of lids with trichiasis from half or more of the lid width. These differences were not significant overall (Table II). Losses to follow-up and duration of follow-up were comparable by allocation, but operative success was significantly different (Table III). This was also apparent after correcting for treatment crossovers (Table IV).

Bilamellar tarsal rotation was significantly more successful than eversion splinting

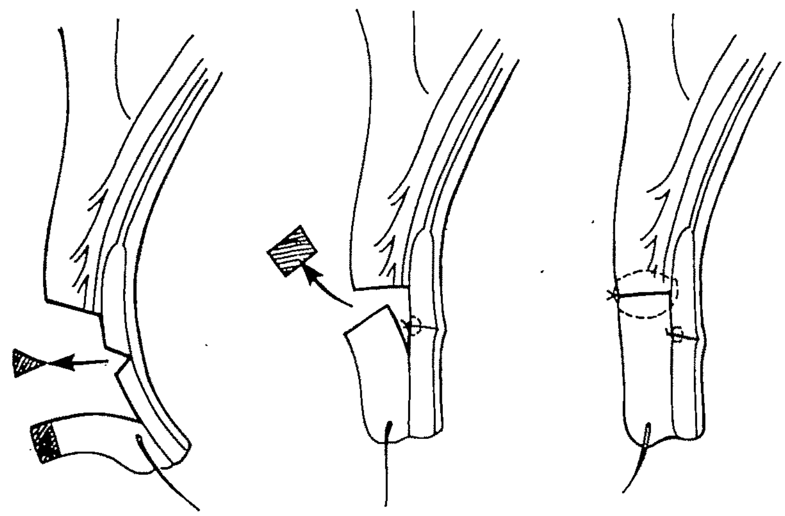

*Figure 1E: Tarsal grooving.*

TABLE I *Lid closure and history of previous surgery in 197 trachomatous upper eyelids with major trichiasis and defective lid closure*

| | *Lid closure defect* | | |
|---|---|---|---|
| | *Yes* | *No* | |
| History of previous surgery: | | | |
| Yes | 29 | 39 | 68 |
| No | 3 | 126 | 129 |
| Total | 32 | 165 | 197 |

Odds ratio=31, 95% CI (9,108)

TABLE II *Previous surgery and extent of major upper lid trichiasis by allocated operation*

| | Bilamellar tarsal rotation | Tarsal advance and rotation | Eversion splinting | Tarsal advance | Tarsal grooving | Total |
|---|---|---|---|---|---|---|
| Enrollment | 41 | 24 | 24 | 41 | 35 | 165 |
| Past surgery: | | | | | | |
| No (%)* | 12 (29) | 8 (33) | 5 (21) | 11 (27) | 3 (9) | 39 (24) |
| Trichiasis ⩾½ lid width: | | | | | | |
| No (%)† | 30 (73) | 11 (46) | 14 (58) | 23 (56) | 25 (71) | 103 (62) |

*$\chi^2=6\cdot7$, df 4, $p>0\cdot1$.
†$\chi^2=6\cdot9$, df 4, $p>0\cdot1$.

TABLE III *Follow-up and outcome of five operations for major upper lid trichiasis from trachoma by operation allocated*

| | *Bilamellar tarsal rotation* | *Tarsal advance and rotation* | *Eversion splinting* | *Tarsal advance* | *Tarsal grooving* | *Total* |
|---|---|---|---|---|---|---|
| Enrollment | 41 | 24 | 24 | 41 | 35 | 165 |
| Lost to follow-up: | | | | | | |
| No (%) | 2 (5) | 2 (8) | 3 (12) | 3 (7) | 2 (6) | 12 (7) |
| Mean time of follow-up: | | | | | | |
| Months | 7·4 | 8·8 | 8·7 | 7·5 | 7·7 | 7·9 |
| Range | 5–10 | 8–10 | 5–11 | 5–10 | 5–10 | 5–11 |
| Success: | | | | | | |
| No (%)* | 29 (71) | 11 (46) | 7 (29) | 11 (27) | 4 (11) | 62 (38) |

*$\chi^2=32\cdot8$, df 4, $p<0\cdot001$.

TABLE IV *Crossovers from allocated operations and outcome by operation done*

| | *Bilamellar tarsal rotation* | *Tarsal advance and rotation* | *Eversion splinting* | *Tarsal advance* | *Tarsal grooving* | *Total* |
|---|---|---|---|---|---|---|
| Enrollment | 41 | 24 | 24 | 41 | 35 | 165 |
| Crossovers from: | 0 | 1 | 0 | 1 | 3 | 5 |
| to: | 3 | 0 | 1 | 1 | 0 | 5 |
| Final numbers | 44 | 23 | 25 | 41 | 32 | 165 |
| Success (%)* | 30 (68) | 10 (43) | 8 (32) | 11 (27) | 3 (9) | 62 (38) |

*$\chi^2=31\cdot1$, df 4, $p<0\cdot001$.

($\chi^2=7\cdot035$, $p<0\cdot01$); tarsal advance ($\chi^2=12\cdot38$ $p<0\cdot001$), and tarsal grooving ($\chi^2=23\cdot74$, $p<0\cdot001$), but not significantly more successful than tarsal advance and rotation ($\chi^2=2\cdot87$, $p>0\cdot05$) (Fig 2). Bilamellar tarsal rotation was the most successful operation regardless of previous surgery, extent of trichiasis preoperatively, and surgeon (Table V).

First operations and lids with trichiasis from less than half the lid margin had higher rates of success, with the exception of eversion splinting and previous surgery (Table V). Failures were least severe for bilamellar tarsal rotation and tarsal advance and rotation, most lids having five or fewer lashes at follow-up, whereas major trichiasis recurred in a large proportion of lids that underwent the remaining three operations (Table VI). Defective lid closure developed only after bilamellar tarsal rotation and tarsal grooving (Table VI).

Of 32 lids with defective lid closure at enrollment 26 (81%) were followed up between four and 10 (mean 7) months after tarsal advance. Two (6%) were successfully treated. Nine (28%) had relief of eye lash/eye ball contact, and 10 (31%) had lid closure restored.

## Discussion

The present study is the first to report a randomised trial of eye lid surgery for tachomatous trichiasis. A simple preoperative grading scheme and postoperative criterion of treatment success were used, the grades depending on the number of lashes making contact with the eye ball and gentle lid closure. This is in accord with the current World Health Organisation system for the assessment of trachoma and its complications, in which trichiasis is defined as the presence of any eye lash/eye ball contact regardless of entropion[10] and on recognition of the importance of defective lid closure.[11] Our minor trichiasis grade was defined by five or fewer lashes, as we had found this to be the number readily treated with electroloysis. The major grade was subdivided by the extent of trichiasis, if localised to less than half, or involving half or more of the lid margin. This subdivision has been previously described.[5]

The operative groups were comparable for factors likely to influence outcome, previous surgery, extent of trichiasis, and follow-up. Enrollment was unequal, as may be expected with randomised allocation in which a blocking procedure is not used.[12]

The outcome with lids grouped by operation allocated and by operation done was similar, as crossovers from allocated operations were few (Tables III and IV). Bilamellar tarsal rotation and tarsal advance and rotation were the most successful operations. The pattern of successful outcomes for all operations was similar after stratification by factors likely to influence outcome – namely, previous surgery, extent of preoperative trichiasis, and surgeon (Table V). The same pattern was observed when operative failure is considered in which the more successful operations had less severe failures (Table VI). The difference of success rate between surgeons was less marked than Table V would suggest:

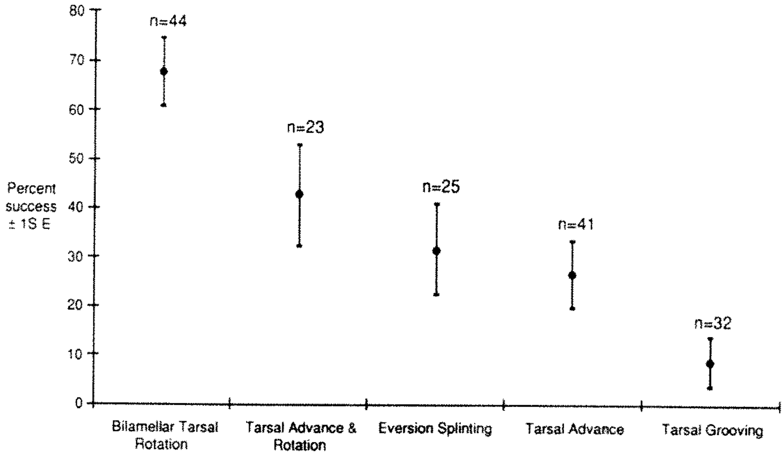

*Figure 2: Proportion of successful results for five operations for upper lid trichiasis from trachoma.*

firstly because failures for bilamellar tarsal rotation and tarsal advance and rotation mainly comprised only one or two lashes at the lateral canthus; and, secondly, because a higher proportion (50%) of lids undergoing bilamellar tarsal rotation by surgeon 2 had undergone previous surgery.

We encountered no serious side effects with any of the operations, but two minor complications were seen with bilamellar tarsal rotation – overcorrection and granuloma formation. One lid was overcorrected, with the distal fragment being rotated 180° back on to the proximal part of the lid. The wound was reopened and resutured with less tension four days after the initial procedure. Overcorrection after bilamellar tarsal rotation is caused by excessive tension of eversion sutures or a too large marginal fragment.[13] Two lids developed granulomas at the tarsal incision, which did not recur after excision. Ischaemic necrosis of the marginal fragment has been suggested as a possible complication of bilamellar tarsal rotation but was not observed.[14] The effectiveness of bilamellar tarsal rotation in our series accords with a high (96·7%) success rate reported for a similar tarsal rotation operation.[15]

TABLE V *Outcome of five operations for major upper lid trichiasis stratified by previous surgery, extent of trichiasis, and surgeon*

| | *Operation* | | | | | |
|---|---|---|---|---|---|---|
| | *Bilamellar tarsal rotation* | *Tarsal advance and rotation* | *Eversion splinting* | *Taral advance* | *Tarsal grooving* | *Total* |
| *Previous surgery* | | | | | | |
| Number | 32 | 15 | 20 | 30 | 29 | 126 |
| Success (%) | 23 (72) | 7 (47) | 6 (30) | 9 (30) | 3 (10) | 48 (38) |
| Yes | 12 | 8 | 5 | 11 | 3 | 39 |
| Success (%) | 7 (58) | 3 (37) | 2 (40) | 2 (18) | 0 (0) | 14 (36) |
| *Trichiasis<or≥½ lid width* | | | | | | |
| <½ | 13 | 12 | 11 | 18 | 8 | 62 |
| Success (%) | 10 (77) | 7 (58) | 6 (54) | 5 (28) | 2 (25) | 30 (48) |
| ≥½ | 31 | 11 | 14 | 23 | 24 | 103 |
| Success (%) | 20 (64) | 3 (27) | 2 (14) | 6 (26) | 1 (4) | 32 (31) |
| *Surgeon* | | | | | | |
| Surgeon 1 | | | | | | |
| Number | 31 | 11 | 16 | 31 | 21 | 110 |
| Success (%) | 20 (64) | 4 (36) | 6 (37) | 7 (23) | 2 (9) | 39 (35) |
| Surgeon 2 | | | | | | |
| Number | 6 | 7 | 6 | 9 | 9 | 37 |
| Success (%) | 3 (50) | 2 (29) | 1 (17) | 3 (33) | 1 (11) | 10 (27) |
| Surgeon 3 | | | | | | |
| Number | 7 | 5 | 3 | 1 | 2 | 18 |
| Success (%) | 7 (100) | 4 (80) | 1 (33) | 1 (100) | 0 (0) | 13 (72) |
| *Overall number* | | | | | | |
| Number | 44 | 23 | 25 | 41 | 32 | 165 |
| Success (%) | 30 (68) | 10 (43) | 8 (32) | 11 (27) | 3 (9) | 62 (38) |

TABLE VI *Recurrent trichiasis and defective lid closure at follow-up after five operations for major upper lid trichiasis from trachoma*

| | *Bilamellar tarsal rotation* | | *Tarsal advance and rotation* | | *Eversion splinting* | | *Tarsal advance* | | *Tarsal grooving* | |
|---|---|---|---|---|---|---|---|---|---|---|
| Trichiasis | n | d | n | d | n | d | n | d | n | d |
| None | 31 | 1 | 10 | 0 | 8 | 0 | 11 | 0 | 6 | 3 |
| 1–5 | 6 | 1 | 7 | 0 | 6 | 0 | 12 | 0 | 8 | 0 |
| >5 | 1 | 0 | 1 | 0 | 7 | 0 | 10 | 0 | 9 | 2 |
| Further treatment! | 4 | 0 | 3 | 0 | 2 | 0 | 5 | 0 | 6 | 0 |
| Lost to follow-up | 2 | – | 2 | – | 2 | – | 3 | – | 3 | – |
| Total | 44 | 2 | 23 | 0 | 25 | 0 | 41 | 0 | 32 | 5 |
| | | | | | | | | | n | d |
| Overall total | | | | | | | | | 165 | 7 |

n = Number of lids.
d = Of which d lids had defective lid closure.
! = Epilation (17 lids) or surgery (3 lids) prior to follow up.

Our 32% success rate for eversion splinting with a gauze roll compares poorly with 98·5% originally reported for this operation and might be due to racial and environmental differences between Burma and Oman or to high losses to follow-up in the original report.[5] Inquiry revealed that tarsal grooving had been the most widely performed operation for upper lid trichiasis in Oman. The association between previous surgery and defective lid closure (Table I) could not be taken as proof as a casual relationship between tarsal grooving and defective lid closure, which could be explained at least in part by a primary association between past surgery and severe cicatrising disease. However, at postoperative follow-up 16% of eyes developed defective lid closure after tarsal grooving compared with 5% for bilamellar tarsal rotation and none for the remaining three procedures (Table VI), which does suggest that tarsal grooving may result in defective lid closure. This is plausible, as tarsal grooving was the only operation requiring excision of tissue.

A disparity in the effectiveness of upper lid entropion operations advocated for community based lid surgery[1] has been demonstrated. Bilamellar tarsal rotation and tarsal advance and rotation at short term follow-up are reasonably effective, but eversion splinting, tarsal advance, and tarsal grooving were ineffective. Tarsal advance was also ineffective for defective lid closure.

Operations appropriate for community use should be able to be performed effectively and swiftly by non-specialist medical or paramedical staff with minimal resources. Bilamellar tarsal rotation was found to be simpler and quicker than tarsal advance and rotation. Trachomatous cicatrisation may be progressive in many patients, so that recurent trichiasis may be expected with time in an increasing proportion of lids even after effective surgery. Longer follow up of appropriate operations is therefore still required to evaluate the place of community based trichiasis surgery as a strategy for prevention of blindness from trachoma.

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# Ocular shedding of herpes simplex virus

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**Abstract**

**The presence, frequency, and relationship of ocular and oral shedding of herpes simplex virus to previous herpes keratitis was investigated. This was to determine if a history of herpes keratitis predisposes to shedding of the herpes simplex virus into the tear film and/or mouth. Swabs were collected from the eyes and mouth of two groups of patients thrice weekly over a two- to four-month period. Group A comprised nine patients with a history of herpes labialis, group B 15 patients with a history of herpes keratitis. Herpes simplex virus type 1 was isolated from 1·33% of mouth specimens but was not identified in any of the ocular specimens. There was no significant difference between groups A and B in terms of ocular or oral shedding. Oral shedding appears to be independent of a previous herpes keratitis. The tear film is an unlikely source of virus in persons either with no history of herpes keratitis or between attacks in those patients with a history of previous herpes keratitis.**

Since Buddingh *et al*[1] demonstrated herpes simplex virus (HSV) in the saliva and stools of asymptomatic persons, there have been several well documented reports on the shedding of HSV into saliva.[2-6] While both spontaneous and induced ocular HSV shedding in animals is well established,[7] the situation in humans remains largely unexplored. In 1967 Kaufman *et al.*[2] studied a group of patients with and without a history of HSV labialis (HSVL) and found an incidence of asymptomatic ocular shedding of between 0·79% and 1·4%. In addition they found HSV in the tears and saliva of experimentally infected animals in the absence of a herpetic lesion.[2] There have been no subsequent reports on humans corroborating Kaufman's findings, nor attempts to establish if an association exists between previous herpetic eye disease and subsequent ocular and or oropharyngeal shedding.

The aim of this study was to establish the presence and frequency of ocular shedding, its relationship to previous HSV ophthalmia (HSVO), and the relationship between ocular and oropharyngeal shedding.

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## Materials and methods

### PATIENTS

Two groups of patients were studied.

*Group A.* This comprised nine healthy patients (five males, four females). The average age was 41 years (range 25–67). In all cases the only clinical manifestation of HSV was recurrent herpes labialis, with an average frequency of 2·9 episodes per year (range 1–6 episodes per year).

*Group B.* This comprised 15 healthy patients (10 males, five females). The average age was 49 years (range 19–69). Fourteen patients had experienced previous dendritic keratitis which had been treated at this hospital by a combination of debridement and topical acycloguanosine or idoxuridine (used in only one case). The remaining patient had had a herpetic blepharitis. All patients except three had suffered from recurrent HSVL to give an average frequency of 1·9 episodes per year (range 0–6 episodes per year). Seven patients had had only one clinical episode of dendritic keratitis. The remaining seven patients had had recurrent dendritic keratitis, with two patients having had a subsequent disciform keratitis necessitating the use of topical steroids. The average frequency of recurrent ocular herpes was 0·135 episode per year (range 0·05–0·35 episode per year). The time between the resolved ocular herpetic lesion and entry into the study was 1·5 weeks for 10 patients, and between 1 year and 20 years for the remaining five patients.

### STUDY DESIGN AND SPECIMEN COLLECTION

The study was conducted from October through January 1988–9. Patients had specimens collected on Monday, Wednesday, and Friday of each week. Informed consent was obtained from all patients.

*Tear film swabs.* Preocular tear film was collected by rotation of a swab along the lower fornix to the medial canthus, where it was held to absorb tears for 10 seconds. Care was taken to avoid the corneal epithelium. The 15 patients comprising group B had swabs taken from their previously affected eye. The nine patients comprising group A had swabs taken from each eye. They were, however, placed in only one bottle of transport medium and hence defined as one swab.

*Oropharyngeal swabs.* A swab was rotated along the buccal mucosa and over the mucosa of the hard palate.

All swabs were immediately placed in transport medium and kept on ice prior to inoculation. For group A the transport medium was a 1 ml solution phosphate buffered saline (PBS A) supplemented with 100 U/ml of penicillin, 100 μg/ml of streptomycin (P/S), and 2% fetal calf serum (FCS). For group B a sterile transport medium pack was used (Virocult, UK).

In addition two of the nine patients in group A, patients A3 and A5, rinsed their mouth with a 5 ml collutary of maintenance medium containing medium 199 with Earle's salts (E-199) (Gibco, UK), supplemented with 2% FCS and 2% sodium bicarbonate. The 15 patients in group B had their eyes examined on each visit by slit-lamp biomicroscopy, and all patients had their oropharnyx examined with a torch and tongue depressor for mouth ulceration. In addition the patients were asked to record any other events such as HSVL, upper respiratory tract infections (URTI), and dental procedures.

### VIRUS ISOLATION

Virus was detected within each specimen by the inoculation of specimen fluid into tissue culture tubes containing confluent monolayered Vero cells (Flow Laboratories) previously propagated in growth medium (E–199 supplemented with 5% FCS, 2% sodium bicarbonate, and P/S). Each tube contained $15\times10^4$ cells/ml growth medium prepared 48 h prior to inoculation to allow formation of a monolayer. At inoculation the growth medium overlying the cells was discarded, and 0·2 ml of each specimen was inoculated in duplicate on to the monolayered Vero cells. As a control two test tubes were inoculated with transport medium alone.

Tubes were then kept on rockers at 37°C for one hour, thus allowing viral adsorption, and were re-fed with 0·8 ml of maintenance medium. Cultures were incubated on stationary racks at 37°C and re-fed every other day with maintenance medium and 50 U/ml nystatin. Viral cytopathic effects (CPE) were recorded daily for two weeks under an inverted light microscope. On detection of viral CPE, incubation was allowed to continue until 100% CPE was obtained. Virus was then harvested from these cultures and stored at −70°C.

Isolates were then typed with an immunofluorescent monoclonal antibody (Syva Micro-Trak, USA).

### STATISTICS

Statistical analysis was by means of a Fisher-Yates exact probability test and a Poisson distribution. $P<0{\cdot}05$ was considered significant.

## Results

In total 752 mouth and 752 eye swabs were collected (Table I). There were no eye isolations. Ten mouth swabs were positive for HSV type 1 (1·33% of swabs). None of the patients developed detectable or symptomatic intraoral or eye lesions during the study. There were 19 episodes of HSVL during the study of which two (10·5%) were concurrent with a mouth isolation. Conversely, of the 10 mouth isolations two (20%) were concurrent with HSVL.

### GROUP A

Of the mouth and eye swabs 379 were from this group, to give an average of 42 swabs per patient (range 16–51).

TABLE I *Isolation of HSV from the eye and mouth*

| | *No of swabs* | *Mouth isolations* | *Eye isolations* | *No of HSVL during study** |
|---|---|---|---|---|
| Group A | 379 | 7 | 0 | 11 (2) |
| Group B | 373 | 3 | 0 | 8 (0) |
| Total | 752 | 10 | 0 | 19 (2) |

*The figures in brackets refer to the incidence of HSVL lesions which were concurrent with a mouth isolation.

*Mouth specimens.* Seven swabs were positive for HSV-1 (1·85% of swabs): five isolations were from patient A5 (10% of his swabs), and two from patient A4 (4·5% of his swabs). None of these isolations were in clusters. Five of the mouth rinses from patient A5 were positive for HSV type 1 (these were concurrent with the positive mouth swabs from this patient).

None of the mouth rinses from patient A3 were positive. Two of the isolations were associated with a concurrent episode of HSVL (28·6% of isolations). Three isolations were associated with a URTI, leaving two isolations not associated with any event.

*Eye specimens.* There were no isolations.

*Associated events.* There were 11 episodes of HSVL (range 0–3), of which two were associated with a mouth isolation (18·2%). There were two episodes of an URTI without concurrent HSVL, which were associated with three of the isolations.

### GROUP B

A total of 373 swabs were collected from this group to give an average of 25 swabs per patient (range 13–42).

*Mouth specimens.* There were three isolations (0·8% of the 373 swabs): one was from patient B7 (5% of his swabs) and two from B2 (6·25% of his swabs). None of the isolations were associated with any event.

*Eye specimens.* There were no isolations.

*Associated events.* There were eight episodes of HSVL and one of URTI, none of which were associated with an isolation.

### GROUP A AND B COMPARED

Although the average number of swabs per patient was higher in group A (42·1) than in group B (24·9), the compliance rate (actual number of attendances/expected number of attendances) was on average above 80% for both groups. Whereas a patient in group A attended on average for 14 weeks, a patient in group B attended on average for eight weeks before leaving the study. There was no significant difference in the number of mouth isolations between groups A and B (Fisher-Yates exact test, $p=0{\cdot}35$).

There was no significant difference in the number of eye isolations from either group; it was zero for both groups. A Poisson distribution was used to assess further the significance of the results. The results from those patients with mouth isolations were then tested using a mean of 10/752 S (S is the number of swabs taken from the patient under question) for a significantly high number of mouth isolations. Only patient A5 had a significantly high number of mouth isolations (Poisson distribution, $p=0{\cdot}0006$).

Group A was then compared with group B without the inclusion of patient A5. There was still no significant difference in the number of mouth isolations between the two groups (Fisher-Yates exact test, $p=0{\cdot}56$).

## Discussion

This study confirms the findings of previous authors in that aymptomatic shedding of HSV can occur in the mouth.[1-6] Although the frequency of oral shedding in this study is less than that of Spruance (7·6%),[3] Douglas and Couch (4·6%),[5] Buddingh *et al* (7%),[1] and Hatherley *et al* (9·6%),[6] it is similar to that of Kaufman *et al* (1·5%).[2] When Buddingh and colleagues' series is considered for adults only, the frequency is decreased to 2·5%.[1] The lower frequency of mouth shedding is unlikely to have been due to the use of swabs, as the isolation of HSV in the two patients who had concurrent swabs and mouth rinses was identical. In additon care was taken to swab the mucosa of the hard palate.[8,9]

All the isolations in this study occurred as solitary events – that is, the minimum interval between isolations was two weeks. In Spruance's study only 38% of isolations occurred as solitary events, with the remaining 62% occurring in clusters.[3] Thus frequency of isolations in his study which occurred as solitary events was 2·8%, which is commensurate with our findings.

None of the patients that we studied had dental procedures. This factor, in addition to a lower frequency of recurrent HSVL (2·3/yr as compared with 4·4/yr reported in Spruance's study[3]) may have contributed to the lower frequency of mouth isolations. There was no significant difference in the prevalence of mouth shedding between groups A and B; thus the rate of asymptomatic oral shedding is independent of previous herpetic keratitis. Reactivation and subsequent shedding in the mouth can occur with a herpes labialis lesion but is largely independent of it. The numbers of mouth isolations that were concurrent with a HSVL lesion (20%) was similar to those previously reported.[3,4]

HSV was not isolated from the tear film of patients with or without a history of herpetic keratitis, and so with respect to ocular shedding groups A and B are identical. That is, a previous history of herpes keratitis does not appear to predispose to the shedding of HSV into the tear film in the asymptomatic state.

It is unlikely that the absence of detectable shedding was due to the use of swabs as opposed to an eye bath, as there is no difference in the detection rate between these two techniques.[7] The effect of treatment, however, during the previous acute attacks needs to be considered; 14 patients in group B had their dendritic ulcers treated by a combination of mechanical debridement and topical acycloguanosine. It has been shown that this combination tends to reduce the recurrence rate following primary ocular herpes, while a lower rate of isolation of HSV from corneal discs has been demonstrated in patients treated with acycloguanosine.[10,11] These factors may have had a role in the absence of ocular shedding in this study.

The significance of oral shedding in relation to HSVO is unknown. A person who is a mouth shedder would probably have been shedding and expectorating virus for some time. But the risk of a mouth shedder or their consort developing HSV keratitis is at present unknown, and to answer this would require a long term prospective study.

The absence of ocular shedding as demonstrated in this study would suggest that the tear film is an unlikely source of virus in persons either with no history of herpetic keratitis or between attacks in those patients with a previous history of herpes keratitis.

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## MINI REVIEW

# Pneumoretinopexy: a personal view

The use of intravitreal air as an adjunct to retinal detachment was first used seriously by Rosengren about 60 years ago. When scleral buckles were later used to close breaks and to relieve vitreoretinal traction the use of air became much less popular. Development both of pars plana vitrectomy and of gases capable of intraocular expansion has reactivated great interest in the use of such gases. The use of expanding gases as part of pars plana vitrectomy to hold the layers of the retina together, while apposition is secured by the use of a laser or cryotherapy induced adhesion, is well accepted. However, the use of such gases for the treatment of retinal detachment without pars plana vitrectomy or of scleral buckling (pneumoretinopexy) is much more controversial, and is now attracting much interest, livening up a rather quiescent retinal detachment scene.

Pneumoretinopexy relies on the capacity of an intraocular gas bubble to tamponade a retinal break, and by doing so, effectively closes the break and results in retinal reattachment without a scleral buckle. In addition to break closure, the gas bubble may also act by relieving dynamic vitreoretinal traction on the break; retinal redetachment is prevented by adhesion produced by cryotherapy or argon laser. Clinical guidelines have been suggested for cases suitable for this procedure. The most favoured gas is perfluoropropane ($C_3F_8$), which will expand four times its original volume after injection into the eye, and thus only a small volume needs to be used. For best results, the retinal break(s) must be in the superior part of the retina – that is, allowing closure from the rising gas bubble – but must not be too large, and if multiple the breaks must be close together. Cases with extensive proliferative vitreoretinopathy are not suitable.

After the injection the patient must be capable of following a demanding postoperative regimen so that the break is in the uppermost position, maintaining this posture for most of the day for at least five days after injection. The operation, performed under local anaesthetic, is quick and simple, and, although paracentesis is often necessary to combat a high intraocular pressure, admission to hospital is not necessary.

It cannot be claimed that pneumoretinopexy is superior to an entirely extraocular non-drainage retinal detachment procedure. Thus, if the depth of subretinal fluid between pigment and neuroepithelium is not great, there is little risk of inaccurate break localisation or of excessive cryotherapy if the non-drainage technique is used. Even though local scleral buckles (which would be preferred to close simple breaks) may sometimes result in infection, refractive changes, and muscle imbalance, the risk of serious intraocular complications is very small.

On the other hand, in pneumoretinopexy severe intraocular problems consequent to the injection of gas have occurred occasionally (such as vitreous incarceration, subretinal gas, haemorrhage, and others). When, however, the depth between pigment and neuroepithelium is deep enough to make break localisation difficult, success rates with the non-drainage approach fall. In these cases, does pneumoretinopexy compare favourably with the drain, air injection into the vitreous, cryotherapy, and explant surgical sequence (D-ACE) that may be used for the management of these cases? The latter approach has as a disadvantage the potential intraocular complications of vitreous injection and of the drainage of subretinal fluid, as well as the extraocular ones related to scleral buckling.

In a recent painstaking and thorough study[1] a randomised comparison between pneumoretinopexy and conventional scleral buckling was made. It was not possible to deduce if some of these cases could have been treated by the non-drainage method, and the great majority of cases in the conventional scleral buckling group were treated with encirclement, drainage of subretinal fluid and in about a third of the cases, an injection into the vitreous cavity. The most important aspect of the study was that in the pneumoretinopexy group reattachment with either one procedure or with subsequent added cryotherapy or laser was achieved in 79·6% of cases. In the scleral buckling group reattachment was advised in 82·2%; so there was no real difference between the groups. In both groups higher reattachment rates were achieved with further procedures.

A recent study was made of 66 cases of retinal detachment in which there was deep subretinal fluid between the retinal break and the pigment epithelium (i.e. not suitable for non-drainage scleral buckling).[2] Other clinical features of these cases – namely, single or breaks close together in the upper half of the retina in cases without proliferative vitreoretinopathy – would otherwise have made them suitable for consideration for pneumoretinopexy. The cases were all treatment by the D-ACE surgical sequence, and a figure of 85% reattachment was achieved with one operation. This incidence seems to be very similar to that in Tornambe and Hilton's groups.[1] However, in the latter study,[1] although the incidence of missed (or less likely new) retinal breaks was worryingly higher in the pneumoretinopexy group, an important and challenging finding was that the return of visual acuity following recent macular detachment was better in those cases treated by pneumoretinopexy than in the scleral buckling group. This aspect needs further study.

In many parts of the world the relatively simple sorts of retinal detachments being discussed are treated by general ophthalmologists who, working in hard pressed conditions, might welcome the procedure of pneumoretinopexy for the wrong reasons – namely, apparently a quick simple procedure without the need for expensive hospitalisation and without the risk of inaccurately localising a scleral buckle. However, the opportunity to examine the retina under relaxed operative conditions (an opportunity welcomed by most retinal experts) is lost and with it the chance to find previously undetected retinal breaks. These breaks will result in redetachment when the gas bubble is absorbed and result in an uncomfortably high failure rate in the hands of the inexpert practitioner.

At present it would seem correct to advocate non-drainage surgery when there is little risk of inaccurate buckle localisation. When this risk rises, it remains to be seen if pneumoretinopexy is superior to other methods such as the D-ACE surgical sequence, as judged by both anatomical reattachment and visual outcome.

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CASE REPORTS

# Infective conjunctivitis and corneal scarring in three brothers with sex linked hypogammaglobulinaemia (Bruton's disease)

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## Abstract

**The ocular findings in three brothers with Bruton's disease are reported. All three boys had purulent conjunctivitis, but the two older brothers also developed marked corneal scarring with visual impairment. *Haemophilus influenzae* was cultured from conjunctival swabs; it was resistant to neomycin but sensitive to chloramphenicol. Tear analysis showed that the three subjects had normal levels of lysozyme but no detectable IgA.**

In 1952 Lieutenant-Colonel Ogden C Bruton, an American paediatrician at the Walter Reed Army Hospital, described a boy with recurrent infections and absent serum immunoglobulins.[1,2] Bruton's disease comprises sex linked hypogammaglobulinaemia, in which there is an inherited defect in B lymphocyte maturation, with consequent failure of antibody production.[3-5] Diagnosis depends on the very low levels of all classes of immunoglobulins, the absence of circulating B cells, and a possible family history of affected male relatives.

Sex linked hypogammaglobulinaemia is a rare disease, accounting for a minority of cases of primary hypogammaglobulinaemia. Boys with the condition generally present with severe respiratory tract infections between 4 months and 2 years of age. The delay in onset of symptoms is due to transplacental passively acquired maternal antibody, which provides initial protection against micro-organisms. Infection is generally with bacteria such as *Streptococcus pyogenes*, *Haemophilus influenzae*, or *Neisseria meningitidis*, reflecting the role of antibody in opsonisation of encapsulated bacteria. In addition, patients with primary hypogammaglobulinaemia are susceptible to mycoplasma infections of the lungs, joints, and urinary tract, as well as chronic echovirus encephalitis/myositis.[6-10]

The treatment of Bruton's disease consists of lifelong immunoglobulin therapy, generally given as weekly intramuscular injections or three-weekly intravenous infusions. Infective episodes should be countered by aggressive antibiotic therapy, and postural drainage is beneficial for expulsion of purulent sputum.

The ocular complications are scantily documented.[11,12] The Medical Research Council study of hypogammaglobulinaemia in the UK (1955–70) describes conjunctivitis and blepharitis, together with more serious recurrent corneal ulceration and keratitis, as occasional presenting features of antibody deficiency.[13] In a study of primary immunodeficiency diseases Franklin *et al* noted three cases of Bruton's disease with non-follicular, non-purulent conjunctivitis associated with a superficial keratitis.[14] From one of these cases *Haemophilus influenzae* type b was isolated.

## Case reports

We consider three Caucasian brothers with Bruton's disease, the mother having the two older sons (aged 11 and 9 years) from a first marriage and the youngest son (aged 9 months) from a second marriage. The mother was unfortunate in that all three of her offspring were affected males. All three boys had marked hypogammaglobulinaemia involving all immunoglobulin classes, and lymphocyte surface marker analysis revealed absent mature B cells.

The oldest boy presented at the age of 3½ years. He had a chronic cough and had developed a septic arthritis in the right knee. Staphylococcus was cultured from the joint, and serum antibody deficiency was detected (IgG 0·01 g/l, IgA 0·05 g/l, IgM 0·05 g/l). After initial treatment with intramuscular flucloxacillin and oral fucidin, followed by three-weekly replacement intravenous immunoglobulin, his joint and respiratory symptoms settled. The middle brother developed an effusion on his right knee at age 3 years and a perianal abscess at 6 years, but has otherwise remained well on immunglobulin therapy. The youngest brother began immunoglobulin therapy at age 6 months and remains healthy. On therapy all three brothers have maintained serum IgG levels at >4 g/l.

The older two boys have had episodic purulent conjunctivitis with associated photophobia over a three-year period, while the youngest boy has had two episodes of mild conjunctivitis. *Haemophilus influenzae* was repeatedly cultured from conjunctival swabs. The two older brothers were initially treated with a course of chloramphenicol ointment for a fortnight, followed by neomycin ointment when required. Despite apparently slight conjunctival inflammation and discharge both older boys have developed marked corneal scars. The oldest boy has

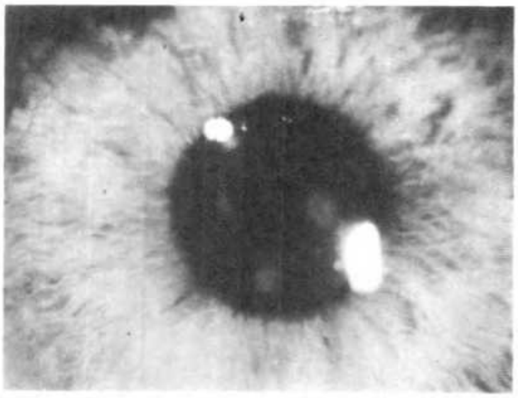

*Figure 1: External photograph of cornea of oldest brother showing multiple central corneal opacities.*

multiple, stromal corneal scars bilaterally, with vision at 6/12 in each eye (Fig 1). The middle boy has a central corneal scar, with 6/36 vision on the right, but no scars and 6/12 vision on the left. The youngest brother has had two episodes of haemophilus conjunctivitis, but has no corneal scarring. All three brothers were treated with a one-month course of ocular chloramphenicol ointment, resulting in their conjunctivae being free from inflammation. The boys were then given a one-week course of oral trimethoprim together with ocular chloramphenicol.

## Material and methods

Single radial immunodiffusion (Mancini technique) was used to measure immunoglobulins (IgG, IgA, and IgM) in tears and saliva, while double diffusion (Ouchterlony technique) determined the presence or absence of secretory component in tears and saliva.

Quantitative estimation of lysozyme in tears was undertaken by measuring the lysis of *Micrococcus lysodeikticus* (Sigma).[15] Human milk lysozyme (Sigma) was used as reference standard. M. lysodeikticus (10 mg) was dissolved in phosphate buffer (pH 6·24, 10 ml) and incubated at 4°C for 2 hours. This suspension (0·5 ml) was added to agarose (Miles, 1·7% in phosphate buffer, 4·5 ml boiled for 5 min and cooled to 56°C). The mixture was poured on to glass plates and allowed to set, before wells were cut with a punch (5 µl well volume). Samples (5 µl) were applied to wells and incubated for 90 min at 37°C. The diameter of the circle of lysis round wells was measured (the mean of two perpendicular graticule readings) in relation to the calibrant titration.

Conjunctival swabs were directly spread on blood agar and mycoplasma media. Blood agar plates were incubated aerobically and anaerobically. Conjunctival swabs were transported in chlamydia transport medium prior to culture in McCoy cells treated with cycloheximide, followed by modified Giemsa staining for typical chlamydia intracytoplasmic inclusion bodies. *Haemophilus influenzae* isolates were serotyped and biotyped by the Public Health Laboratory Service (PHLS) Haemophilus Reference Unit at the John Radcliffe Hospital, Oxford.

TABLE I *Levels of immunoglobulins (Ig), secretory component (SC), and lysozyme in tears from three brothers with X-linked hypogammaglobulinaemia*

| *Patient* | *IgG* | *IgA* | *IgM* | *SC* | *Lysozyme* |
|---|---|---|---|---|---|
| Oldest brother | 0·04 (0·05) | ND (0·54) | ND | Present | 2·0 (1·0) |
| Middle brother | 0·03 (0·04) | ND (0·42) | ND | Present | 1·0 (0·96) |
| Youngest brother | 0·02 (0·02) | ND (0·17) | ND | Present | 0·65 (0·85) |

Levels are quoted as g/l, with values for an age and sex matched normal control (without ocular disease) given in brackets. ND = not detectable.

## Results

The tear analysis is shown in Table 1.

Initial conjunctival and nasopharyngeal swab cultures from all three boys yielded heavy growths of non-encapsulated *Haemophilus influenzae* of serotype II. Following treatment with 1% chloramphenicol ointment, a light growth of haemophilus remained in the conjunctiva of one boy, the other brothers having negative conjunctival cutures.

## Discussion

Three brothers with Bruton's disease and infective conjunctivitis are presented, the two older boys developing corneal scarring with visual impairment. The conjunctivitis was clinically low grade, with slight purulent exudate and little erythema, but nevertheless corneal scars sufficient to impair vision developed.

Humoral antibacterial activity in normal tears is mainly due to lysozyme and IgA. When males with Bruton's disease receive intravenous immunoglobulin therapy, adequate levels of serum IgG can be achieved, but the serum levels of other immunoglobulin classes are unchanged. Hence patients' tears contain IgG but no detectable IgA, with a conjunctival IgA deficiency possibly contributing to their vulnerability to infective conjunctivitis. However, it must be stressed that patients with selective IgA deficiency are not at particular risk of bacterial conjunctivitis.

Non-encapsulated *Haemophilus influenzae* is present in the nasopharynx of most healthy children but normally constitutes less than 2% of the bacterial flora. Haemophilus may cause both upper and lower respiratory tract infections, as well as sporadic or epidemic conjunctivitis, disturbing immune mechanisms in the eye by production of an IgA protease.[16] Therapy for haemophilus conjunctivitis in Bruton's disease is primarily by a topical antibiotic to which the bacterium is sensitive.

Following treatment with ocular chloramphenicol all three brothers had prompt resolution of their conjunctivitis. However, a light growth of haemophilus remained in one brother, and all three boys are being treated with ocular and oral antibiotics. This is in an effort to eradicate nasopharyngeal carriage, since haemophilus carried in the nasopharynx could ascend the lacrimal duct to reinfect the conjunctiva. Treatment of all three brothers was undertaken to minimise cross infection.

Neomycin-resistant chloramphenicol-sensitive haemophilus was cultured from the conjunctivae of all three brothers. This resistance could have developed after prolonged neomycin therapy, and may be due to drug destroying enzymes such as phosphotransferases and acetyltransferases.

The presence of non-encapsulated strains of biotype II in all three boys suggests that cross infection may have occurred. However, the presence of haemophilus does not prove that the bacterium is directly responsible for the conjunctivitis and corneal scarring.

Our experience suggests that patients with antibody deficiency and haemophilus conjunctivitis may be at risk of developing corneal scarring despite relatively mild conjunctival symptoms and signs. In these patients we suggest careful microbiological assessment, followed by treatment with suitable ocular and oral antibiotics, combined with regular ophthalmic review.

We are grateful for the assistance of Dr J B Skelton and Dr M P E Slack of the PHLS Haemophilus Reference Unit at the John Radcliffe Hospital, Oxford.

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# Posterior scleritis as an intraocular tumour

Paul T Finger, Henry D Perry, Samuel Packer, Richard A Erdey, Geoffrey D Weisman, Patrick A Sibony

## Abstract

**Posterior scleritis rarely presents as a large 'intraocular tumour' and continues to be a challenge in diagnosis and management. We present the case of a 66-year-old male with no known rheumatic disease, pain, proptosis, or diplopia, but with progressively decreasing visual acuity and a large, discrete 'subretinal tumour', 15×17 mm basal diameter and 8·3 mm apical height. Histologically the tumour was shown to be grossly thickened and necrotic sclera.**

Posterior scleritis is difficult to diagnose because of its tendency to present with a variety of symptoms.[1] These symptoms include pain, refractive changes, decreased visual acuity, diplopia, and proptosis.[2-6] Though a history of collagen vascular disease, anterior scleritis, female sex, or serous retinal detachment can aid in the diagnosis, none is universally characteristic.[6] When posterior scleritis presents as an 'intraocular tumour', A- and B-scan ultrasonography showing relatively high internal reflectivity, thickened sclera, and retrobulbar oedema may be the most useful ancillary tests.[4 5]

## Case report

A 66-year-old while male presented with a five-year history of 'red eyes' and a two-year history of decreased vision OS. He had a history of a transient episode of polyarthritis and unexplained jaundice five years before presentation, blepharitis in both eyes, and glaucoma in the left eye.

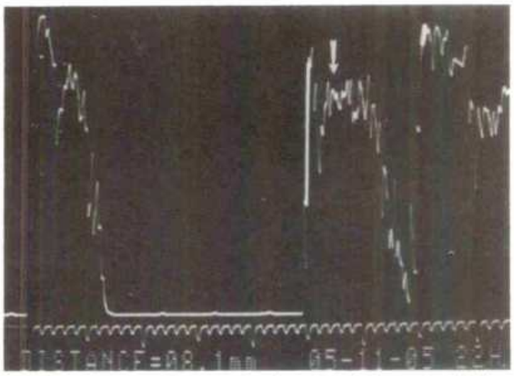

*Figure 2: A-scan echogram showing an apical tumour height of 8·1 mm, and relatively high intratumor reflectivity (arrow).*

Ophthalmic examination revealed a visual acuity of 20/25 OD and 20/200 OS, an afferent pupillary defect OS, full ocular motility, and applanation tensions of 14 OD and 12 OS. Slit-lamp examination showed a mild seborrhoeic blepharitis, conjunctival injection, mild scleral thinning 4 mm posterior to the superonasal limbus OS, and posterior subcapsular cataracts OU. Indirect ophthalmoscopy revealed vitreous cells, a large, non-rhegmatogenous retinal detachment in the superonasal quadrant, and an underlying orange-white tumour 15×17 mm in basal diameter and extending to within 3 mm of the optic nerve OS (Fig 1).

A-scan ultrasonography revealed relatively high intratumour reflectivity and a tumour height of 8·1 mm (Fig 2). B-scan ultrasonography showed a subretinal tumour with a multinodular surface, with a non-homogeneous intratumour pattern, surrounded by a retrobulbar echoluscent zone (Fig 3). On fluorescein angiography blotchy hyperfluorescence over the tumour and cystoid macular oedema were noted OS.

Our patient was advised of the possibility that this tumour could be a choroidal melanoma with some atypical characteristics. A metastatic survey was negative and the options of observation, radiation, and enucleation were discussed.

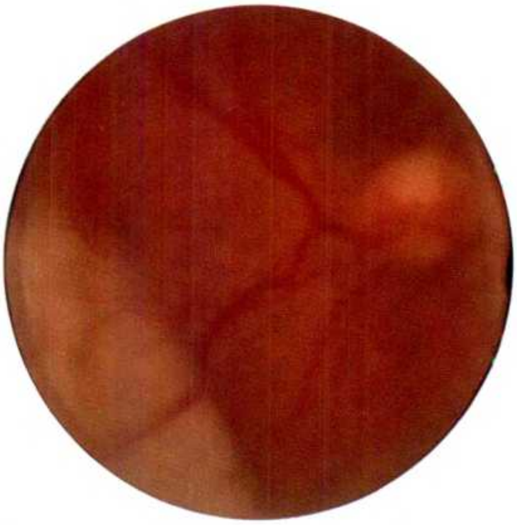

*Figure 1: Through a hazy vitreous an orange-white superonasal subretinal mass extends to within 3 mm of the optic nerve.*

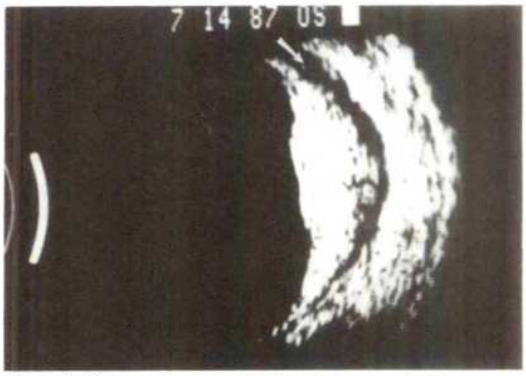

*Figure 3: B-scan echogram showing the intraocular tumour with a multinodular surface, internal reflectivity, and retrobulbar echolucency (arrow).*

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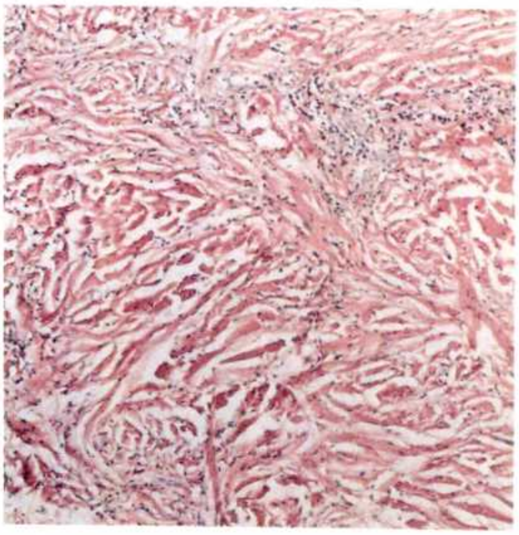

*Figure 4: Histological section revealed diffuse oedema and inflammation separating scleral collagen fibres. (Haematoxylin and eosin, ×35)*

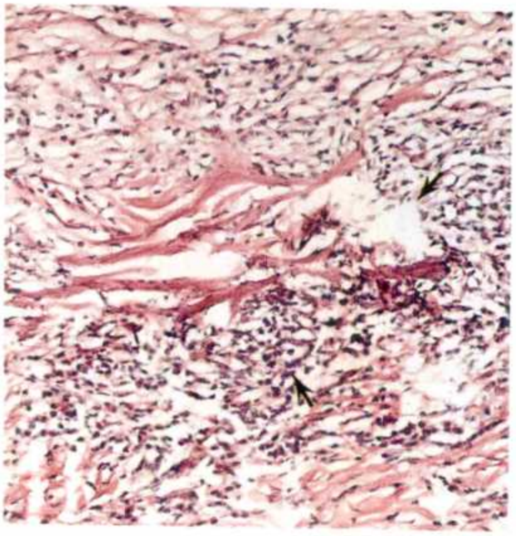

*Figure 5: Histological section demonstrating areas of scleral necrosis and granulomatous infiltrates (arrows). (Haematoxylin and eosin, ×35)*

He chose to be enucleated and have 600 cGy of preoperative external beam radiotherapy.

### PATHOLOGICAL FINDINGS

While scleral thinning was noted superiorly from the 8 o'clock to the 12 o'clock positions running between 4 mm and 8 mm posterior to the limbus, the sclera showed marked thickening in an area measuring 15×17 mm in basal diameter and reaching 8·3 mm in maximal thickness. By light microscopy the intraocular mass was noted to arise from the sclera, which was thickened and infiltrated with inflammatory cells. Diffuse oedema separated scleral collagen fibres (Fig 4), and there were nodular areas of necrosis with a granulomatous reaction next to necrotic sclera (Fig 5). A large serous detachment of the retina was also noted in association with multifocal retinal pigment epithelial detachments.

## Discussion

It is noteworthy that our patient did not have ocular pain. His injected conjunctiva was attributable to blepharitis, and his decreased visual acuity was secondary to cystoid macular oedema, an atypical finding for posterior scleritis.[4] He lacked proptosis, because his 'tumour' had grown into the globe rather than extending into the muscles, cone, and orbit.[4] Though his history of transient glaucoma was consistent with posterior scleritis, he did not have a raised intraocular pressure or anterior segment inflammation at presentation.[4 6]

While indirect ophthalmoscopy revealed a large superonasal orange elevation of the choroid, choroidal folds and retinal striae secondary to diffuse posterior scleral inflammation were notably absent.[4]

Ultrasonography was most consistent with the diagnosis of posterior scleritis. Though the A-scan showed an unusually large intraocular tumour, intratumour reflectivity was very high. This was probably due to the many echodense scleral fibres separated by regions of inflammation and necrosis seen on histological examination (Fig 5). Our B-scan findings were similar to those of Cappaert *et al*,[5] showing thickened sclera and retrobulbar oedema (Fig 3).

In one of the earliest documented cases of posterior scleritis a 49-year-old male presented with a painful red eye, light perception only retinal detachment, and secondary glaucoma, and was diagnosed by enucleation.[6] Our remarkably similar case, occurring over 50 years later, illustrates that, in spite of the modern diagnostic aids of fluorescein angiography and ultrasonography, posterior scleritis as an 'intraocular tumour' remains a diagnostic challenge.

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*British Journal of Ophthalmology*, 1990, **74**: 123–124

# Ciliary body melanoma with optic nerve invasion

Saad Al-Haddab, Ahmed Hidayat, Khalid F Tabbara

**Abstract**

**A case of melanoma of the ciliary body is presented. Initially the patient was diagnosed and treated for uveitis, but following CT scanning and ultrasound a tumour was detected and the eye enucleated. Histopathologically it was found that the tumour had invaded the optic nerve head, apparently via Cloquet's canal.**

Malignant melanomas of the ciliary body are rare.[1-4] In contrast to retinoblastoma, invasion of the optic nerve by uveal melanoma is also rare.[5] This condition was noted in 3·6% of the cases summarised by Reese.[1]

We report herewith a case of ciliary body melanoma that masqueraded as anterior uveitis and invaded the optic nerve.

## Case report

A 20-year-old man presented with a history of decrease of vision in his left eye of two months' duration. He had no history of previous medical or ocular problems. Elsewhere he had been diagnosed as having uveitis. Topical steroids were prescribed, which consisted of prednisolone acetate 1% every two hours. The right eye showed nothing abnormal. The left eye showed a visual acuity of no light perception. Intraocular tension in the left eye was 45 mmHg by applanation tonometry. Pigmented precipitates were seen on the lower quadrants of the corneal endothelium, and there were 2+ cells and a 2+ flare reaction in the anterior chamber. Small, round, yellowish nodules on the iris were seen, with rubeosis at the 3 o'clock position. The pupil was irregular, with a 360° posterior synechia. The lens was cataractous and had pigmentary deposits over its anterior surface. The fundus could not be seen.

A computerised tomographic scan of the left orbit showed a large mass located on the ciliary body nasally, with evidence of choroidal excavation (Fig 1) and thickening of the optic nerve. Ultrasound examination of the left eye showed a large, moderately reflective, slightly irregular mass located at the ciliary body nasally. The patient underwent enucleation of the left eye. Six months after the enucleation the patient had a clear socket without any evidence of recurrence of the melanoma in the orbit.

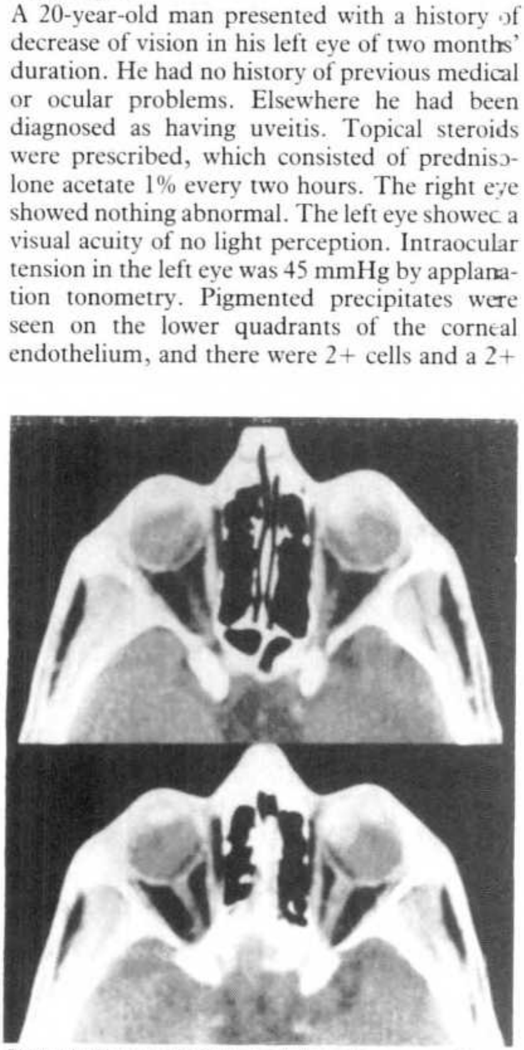

*Figure 1: The upper and lower halves of a composite computerised tomography scan of the left orbit showing the ciliary body mass nasally. The lower half shows slight thickening of the left optic nerve in comparison with the right.*

### PATHOLOGICAL FINDINGS

Grossly a large black ciliary body tumour was located nasally; it measured 10×10 mm at its base and 6 mm in height. Anteriorly there was seeding into the anterior chamber angle and on to the posterior surface of the cornea. Posteriorly there was seeding into the vitreous body behind the lens and into Cloquet's canal in the form of a brown strand that blended posteriorly with a small brown mass covering and obscuring the optic nerve head (Fig 2). The 6 mm optic nerve stump was thickened measuring 5·5 mm in thickness. A cross-section of the optic nerve at the line of surgical transection showed brown discoloration. Microscopically there was a large, heavily pigmented, mostly necrotic, malignant melanoma that involved the ciliary body and a small portion of the adjacent peripheral choroid (Fig 3).

The neoplasm had also invaded the trabecular meshwork, canal of Schlemm, and the collector channels. The small area at the level of pars

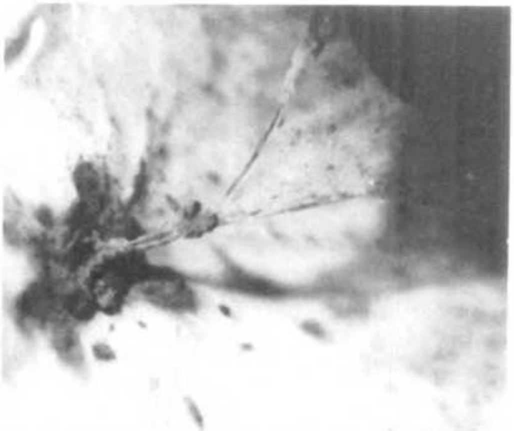

*Figure 2: A brown strand of tumour cells within the hyaloid canal is continuous posteriorly with a brown mass that covers and obscures the optic disc.*

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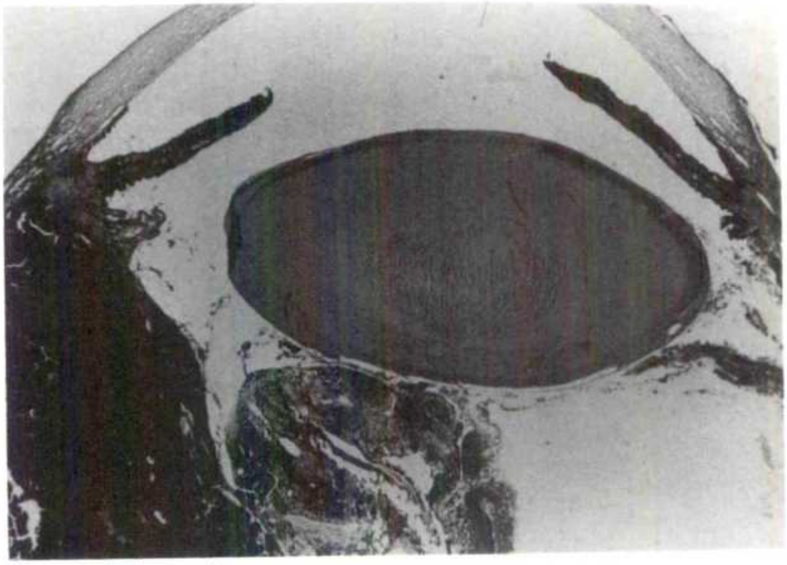

*Figure 3: The large and heavily pigmented ciliary body melanoma is associated with seeding of tumour cells into the vitreous, posterior chamber, and anterior chamber angle.*

plana, where viable cells were present showed a mixture of epithelioid and spindle B cells.

## Discussion

This case of ciliary body melanoma masqueraded as anterior uveitis. The large necrotic area of the tumour is believed to have induced inflammatory response and uveitis. Although retinoblastomas commonly invade the optic nerve, extension of uveal melanoma to the optic nerve is rare. In our patient the tumour cells reached the optic nerve via Cloquet's canal, vitreous body, and retina. Thickening of the left optic nerve was noted by computerised tomography in comparison with the sound eye. Extension of uveal melanoma to the optic nerve occurred in 3·7% of 432 cases reviewed by Shammas and Blodi.[2] The optic nerve can be invaded by a uveal melanoma by direct extension through the vitreous and shedding of tumour cells.[3,4]

A number of factors have been noted to increase the likelihood of extension to the optic nerve. They include raised intraocular pressure, large tumour size, diffuse growth pattern, epithelioid cell type, tumour necrosis, glaucoma, and peripapillary location.[2-4] Another important factor which made the prognosis worse in our patient was invasion of the collecting channels.

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# LETTERS TO THE EDITOR

## Chart for visual acuity screening

SIR,—I read with great interest the paper by Wong and Kaye on a suggested chart for visual acuity screening.[1] However, I was surprised to find that they recommended widespread clinical use of this chart without any clinical data to confirm its suitability. The statistical argument they use is compelling, but surely a comparison with other methods of acuity testing should be undertaken to confirm both its efficacy and its potential for rapid testing?

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1 Wong D, Kaye SB. Chart for visual acuity screening. *Br J Ophthalmol* 1989; **73**: 457–60.

SIR,—The most widely used visual acuity chart in the United Kingdom, namely, the Snellen chart, has questionable theoretical foundations, its credence lying in its widespread use. Indeed its design disqualifies it from being used as either a reference or a comparative chart in any proposed clinical trial. That is, the variable number of letters per line leads to a varying and often indeterminate threshold per line – for example, part scores and interline comparison.

Because of these considerations the NAS-NRC recommended a chart containing 10 letters per line.[1] The Ferris chart is a modification of this, but in addition it is logarithmically progressive from line to line, each line having a similar difficulty score.[2]

These two charts have their value in that they are specific and have attained credence not from comparison with other charts but from their sound theoretical foundation. The chart proposed in our paper[3] uses the same stimuli and is constructed in much the same way as the latter two charts. It is designed for screening purposes and differs by having only two equivalent letters per line. As discussed in the article, reducing the number of letters per line minimises testing time without significantly altering the sensitivity of the chart, provided the letters of any pair are equivalent and the end point stringent – that is, both offers need to be correctly identified. What is proposed is not a new method for recording visual acuity but a new convention for defining the end point.

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1 NAS-NRC Committee on Vision. Recommended standard procedures for the clinical measurement and specification of visual acuity. *Adv Ophthalmol* 1980; **41**: 103.
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# NOTES

## Ocular pharmacology

An international symposium will be held on 'Ocular pharmacology and therapeutics' at New Delhi, India, on 8–10 August 1990. Details from Dr S K Gupta, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110 029, India.

## Paediatric ophthalmology

A course on paediatric ophthalmology will be held on 10–15 September 1990 at Nadi al Bassar North African Centre for Sight Tunis. Details from Nadi al Bassar, 9 Boulevard Bab Menara, 1008 Tunis, Tunisia.

## Panhellenic Ophthalmological Society

The society will hold the following congresses in 1990. 7 April: Spring Symposium, with main topic 'Management of unilateral aphakia in children and young adults'; at Patra, Greece. 30 May: 3rd Annual Meeting (educational courses), with main topics: (1) Trauma, (2) Refractive surgery, (3) Contact lenses, (4) Neuro-ophthalmology; at Thessaloniki, Greece. 8 September: Current Concepts in Ophthalmology, with main topic: 'Management of cataract-glaucoma'; at Athens, Greece. Further information from: Panhellenic Ophthalmological Society, University Eye Clinic, AHEPA Hospital, Thessaloniki, Greece.

## Cataract congress

The Welsh Cataract Congress 1990 will be held on 13–16 September 1990. Details from Eula Mae Childs, Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin (NC 200), Houston, TX 77030, USA.

# BOOK REVIEWS

**Clinical Ocular Oncology.** By Devon H Char. Pp. 402. £130·00. Churchill Livingstone: Edinburgh, 1989.

Only one previous author has attempted to cover the entire field of ocular oncology in a single volume. Algernon B Reese included tumours of the eyelid, conjunctiva, orbit, and eye in his classic book, the last edition of which appeared in 1976. It is to the credit of the present author that he has succeeded in repeating this mammoth task in a slimmer volume.

Most textbooks of ocular oncology published so far have tended to concentrate on differential diagnosis and pathology. To some extent this approach has tended to conceal a relative lack of knowledge and understanding of how best to manage patients with ocular and adnexal tumours. Since Reese's time diagnostic and treatment approaches have changed dramatically with the advent of ultrasound, computerised tomography, and magnetic resonance imaging, with improvements in scleral plaque radiotherapy, and with the arrival on the scene of charged particle radiotherapy using protons and helium ions. There is now a great deal of information in the literature on the efficiacy of these newer methods of diagnosis and treatment, and Dr Char has chosen wisely to depart from the tradition to include detailed pathology so as to accommodate adequate discussion of the clinical aspects. The result is a very practical text with its emphasis on diagnosis and management.

This well referenced book benefits from a wealth of illustrations, many in colour, which show clearly the clinical and diagnostic scan appearances of all the common ocular and adnexal tumours and which include diagrams of operative techniques and photographs of surgical instrumentation and radiotherapy equipment. These, and its clear layout, will find favour with general and specialist ophthalmologists and residents in training alike.

JOHN HUNGERFORD

**Current Neuro-Ophthalmology.** Eds. Simmons Lessell and J T W van Dalen. Pp 370. £64.00. Churchill Livingstone: Edinburgh. 1988.

This practical volume provides an authoritative review by 27 authors of recent advances in neuro-ophthalmology. The critical analysis is provided in six sections, with the largest section being devoted to the sensory visual system. Thus the differential diagnosis of optic neuritis is considered (Currie) and then tumours of the optic nerve (Kennerdell). Radiotherapy is recommended for nerve sheath meningiomas and optic nerve sheath biopsy/decompression for idiopathic lesions. The importance of a small optic disc has been confirmed as a predisposing factor in anterior ischaemic optic neuropathy, though there are no conclusive thoughts on treatment (Behrens). Succeeding chapters discuss the chiasm, retrochiasmal pathways, and higher visual functions.

The ensuing five chapters discuss aspects of ocular movements, including the eyelid, the neural integrator, nystagmus, supranuclear disorders and non-myasthenic ophthalmoplegia. These chapters are up to a good standard, have an extensive bibliography, and reflect the current state of the art. In a 15-page review of the pupil Thompson discusses autonomic disturbance and concludes with tadpole pupils. Final chapters deal with more specific subjects, such as the orbit, myasthenia, facial pain, and neuroradiology.

This remains a very useful volume and has a prime function of introducing recent advances and current thoughts in neuro-ophthalmology. All the authors are experts in their field, so that the review of the literature includes a critical and advisory function. The practising neuro-ophthalmologist will find this book essential, but the clinical ophthalmologist will also find it an extremely good source of reference.

M SANDERS

**Manual of Glaucoma: Diagnosis and Management.** By Theodore Krupin. Pp. 257. £32·50. Churchill Livingstone: Edinburgh, 1988.

This short text sets out to provide a basic guide to the identification and treatment of the glaucomas. The authors state that it arose from resident and postgraduate teaching by staff of the glaucoma service at the Scheie Eye Institute, and it can be seen to be directed towards ophthalmologists at a similar stage of their training.

Although the book is the combined effort of several authors, the style of the text is consistent and easy to read. The page format is double columned, and the points for each section are numbered for easy reference. The diagrams are clear and useful. The pictures, however, are too dark, too few, and add little to the text. Each chapter concludes with a brief further reading list.

The book includes chapters on the basic examination of the glaucoma patient, including a useful summary of the state of the art of computer assisted perimetry. Then follow sections on classification, clinical approach to glaucoma, diagnosis, and medical treatment. Chapters on laser and surgical treatment follow. The book concludes with a short chapter on congenital glaucoma.

In providing this short text the authors have produced an easy to read summary of the glaucomas. There are two areas where the American authorship diverges from British views. The first is the need for a significant section on Schiøtz tonometry together with nomograms for computing of scleral rigidity though this hardly finds a place in routine management today. The second is the decision to devote an entire chapter to tonography, again, with an appendix for tonographic tables. By all means mention these for completeness but point out that this method of examination now has no place in clinical management, whatever its role is in research.

In addition to these points there are a number of differences in emphasis between American and British glaucoma management which could be noted in a European orientated second edition. Direct gonioscopy has little place in clinical examination outside the operating theatre. It would be worth pointing out that it is the glaucoma patient from the Indian subcontinent rather than blacks who develop creeping angle closure glaucoma. In the management of coexisting glaucoma and cataract, glaucoma triple procedures should always be considered when the angle is open, while extracapsular cataract extraction alone could be considered in patients with angle closure.

In the section on congenital glaucoma a common error is to rely on standard anaesthesia for measuring intraocular pressure because this artificially lowers the pressure, yet no mention is made of the commonly used drug ketamine, which does not induce this problem.

Finally, there are a number of misspellings, including aceclidine and, at a later stage of the text, the reviewer's name.

The criticisms noted above, however, are minor and correctable. These could easily be inserted for the second edition to which this book deserves to run.

R A HITCHINGS

**Molecular Biology of the Eye: Genes, Vision, and Ocular Disease.** Eds. Joram Piatigorsky, Toshimichi Shinohara and Peggy S Zelenka. Pp. 471. US$ 96.00. Alan R Liss: New York, 1988.

This book contains the proceedings of a National Eye Institute-UCLA symposium and covers many research areas which are currently using molecular biology techniques. There are sections on phototransduction, evolution of ocular genes such as encoding crystallins and interphotoreceptor retinoid-binding protein (IRBP), gene expression, and differentiation in the lens and retina. Ocular disease is covered in the largest section and describes recombinant DNA mapping of retina pigmentosa genes, the molecular genetics of gyrate atrophy, and Norrie disease. Studies using probes for viruses are discussed, as are the molecular interactions of crystallins in relation to cataract. Oncogenes in both retinoblastoma and the retinal pigment epithelium in proliferative vitreoretinopathy are examined.

This is not an easy book to read, and much of the work presented is written in the jargon of molecular biology, but the discussion summaries at the end of each section are useful.

S LIGHTMAN

**Diseases of the Orbit.** By Jack Rootman. Pp 628. £79.00. Lippincott: London, 1988.

In writing a major text for ophthalmologists and others concerned with the diagnosis and treatment of orbital diseases Dr Jack Rootman has been able to draw on his experience as both a pathologist and an orbital surgeon. This experience is manifest in the orderly and logical development of the text – from a basic surgical anatomy of the orbit, to the ways in which the location and pathophysiology of orbital disease affects its presentation, and finally to a comprehensive, but very readable, review of orbital diseases.

Throughout the text the clinical importance of the various diseases is indicated, this often being supported by epidemiological data drawn from 10 years' personal experience at the University of British Columbia Orbital Clinic. Furthermore, the text is supported by a good bibliography of both recent and past references. Areas of clinical or pathological controversy are presented as a balanced discussion. The chapter on orbital surgery provides a useful outline of techniques, but might not be sufficient to guide the inexperienced surgeon.

As with any new book there are some errors in the text or the illustrations; these are not, however, of such number as to detract from the interest of the book. The high quality of the illustrations reflects the artistic gifts of the author and, when combined with the excellent printing and binding, produces a beautiful book.

Dr Rootman has written an excellent, readable textbook about orbital diseases, the distillation of his talents as an experienced clinician and pathologist. It is an essential addition to any ophthalmic library, and all ophthalmologists with an interest in diseases of the orbit should purchase a copy.

J E WRIGHT

**Diagnosis and Management of Orbital Tumors.** By Jerry A Shields. Pp. 401. £80.00. Saunders: London, 1989

Very few surgeons will encounter more than a handful of orbital tumours in their working year and most will hardly ever see some of the less common neoplasms which arise in the orbit. How then, in the absence of experience, is the clinician to distinguish neoplastic from non-neoplastic lesions and the rare from the commonplace other than by reference to an up-to-date account of the various tumours and related disorders which affect the orbit? This book has been carefully planned and serves such a need very well indeed.

The book is divided into three sections and is generously illustrated with line drawings and with well annotated photographs of the clinical, radiological, and pathological appearance of the tumours it describes. The first section comprises a review of pertinent anatomy, diagnostic techniques, and surgical approaches to the orbit. A description of the method of clinical examination is followed by a chapter which deals succinctly with modern radiological investigations, both non-invasive and invasive, with ultrasonograpy and magnetic resonance imaging, and with various biopsy techniques. It concludes with chapters on basic principles of management and on inflammatory conditions which can simulate neoplasms. The second and third sections consider respectively primary orbital cysts and tumours and metastatic and secondary orbital tumours. In a comprehensive review each specific tumour is systematically discussed under the subheadings of definition and incidence, clinical features, diagnostic approaches, pathology and pathogenesis, management, and prognosis. Each chapter concludes with a brief summary.

The subject of orbital tumours has been approached in an extremely practical manner. The format adopted lends itself to ease both of reference and of study so that this book will be valued by the ophthalmologist in training as well as by the experienced surgeon.

JOHN HUNGERFORD

**Neurology and Neurobiology.** Vol 43. **Dopaminergic Mechanisms in Vision.** Eds Ivan Bodis-Wollner, Marco Piccolino. Pp 276. US $55.00. Alan R Liss: New York, 1988.

The role of dopamine as a neurotransmitter in the central nervous system and its importance in the control of motor behaviour via the nigrostriatal pathways in the basal ganglia is well recognised. There is now increasing evidence of the presence of dopa elsewhere in the nervous system, especially in the retina. In the early 1960s dopaminergic cells were identified in the retina of rats and subsequently in a wide variety of species, including non-human primates and man. A fascinating body of anatomical, biochemical, physiological, and functional evidence regarding dopaminergic mechanisms has accumulated and is reviewed in detail in this book. It is based on the proceedings of the International Brain Research Organisation World Conference in Budapest in 1987. The editors have supplemented these contributions with others from invited authors.

In most species 2–5% of amacrine cells are dopaminergic. The somata are in the inner nuclear layer with dendrites and pre- and postsynaptic terminals in the inner plexiform layer or, in a subset of cells, in the outer plexiform layer. Dopaminergic cells have a widespread distribution over the whole retina, with a density calculated as approximately 20 per mm$^2$ in man. Both D1 (the subgroup increasing adenylate cyclase activity) and D2 (no effect on adenylate cyclase activity) neurons have been demonstrated, and there is evidence for the synthesis, release, and uptake of dopa in the retina. In lower vertebrates dopaminergic neurons are light adaptive modulators of melatonin biosynthesis and retinomotor functions; in higher vertebrates dopamine deficiency – as in monkeys treated with 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) – reduces horizontal cell activity. Retinal dopamine turnover increases with light stimulation. These topics are covered in considerable detail.

Perhaps inevitably in a multiauthored work there is considerable overlap between contributions, especially from the basic scientists, most of whom cover much the same ground in their introductions before describing their experiments. The question of the exact functions of the dopaminergic neurons remains open. There is speculation that they modify the receptive field properties of ganglion cells and are concerned with the tuning and amplification of foveal vision. Clinicians among the contributors describe abnormalities of contrast sensitivity, visually evoked potentials, and the pattern electroretinogram in Parkinson's disease which improve with treatment, but it is not clear that these have any functional significance for the patients.

For the practising clinical ophthalmologist this book is a reminder of the enormous complexity of retinal neuronal function and an interesting insight into the methods used to decode it. It would be an appropriate purchase for any library of visual science.

JOHN ELSTON

**Walsh and Hoyt's Clinical Neuro-Ophthalmology.** 4th Edn. Vol 3. By Neil R Miller. Pp 734. £65.25. Williams and Wilkins: London. 1988.

The third edition of this famous textbook comprised three volumes and contained for most readers all currently available knowledge. The third volume of the 4th edition has now appeared, and we are promised two further volumes to contain vascular disease, trauma, and infectious diseases. Thus our first consideration must be to congratulate the author and admire his ability to gather and display so much knowledge.

The third volume considers tumours of the eye, the orbit, and the brain and related conditions. The first chapter describes the symptomatology of tumours in different sites, and though 90 pages in length there is a bibliography of 15 pages! This is followed by tumours of neuroectodermal origin with a full discussion of the recent state of the art regarding chiasmal and optic nerve gliomas. This is followed by another excellent chapter on meningiomas, with particular emphasis on lesions affecting the anterior visual system. It is sad in some ways that the author has decided to omit to a great extent the use of CT scanning and magnetic resonance imaging in the illustrations, as these tests now play such a vital role in diagnosis and management. Pituitary tumours and craniopharyngioms are covered in great depth in an ensuing chapter. Some of the best illustrated chapters follow, with clinical and numerous pathological illustrations of tumours and vascular anomalies involving the orbit. An interesting chapter well worth perusal when the reader is confronted with a problem case discusses the paraneoplastic syndromes. Finally a favourite with all interested in the medical and paediatric aspects of ophthalmology is a chapter on the phakomatoses. Many will see for the first time a photograph of the leaf of the mountain ash which provides such a characteristic diagnostic sign for tuberous sclerosis.

One could make minor comments about this being an encyclopaedia, with numerous facts and an extensive review of the literature, rather than a critical and advisory clinical textbook. However, this would be to belittle our great gratitude to the author for providing such an outstanding volume for the reader to savour. A worthy successor has therefore been found to maintain and enhance the reputation established by Walsh, and then Walsh and Hoyt. This volume deserves a place on every library bookshelf and I am sure many individual libraries.

MICHAEL SANDERS

**Ophthalmology.** By N R Galloway and S A Vernon. Pp 110. £7.95. Springer-Verlag: London. 1988.

This small book contains 200 multiple choice questions in ophthalmology arranged in five sections to cover introductory anatomy and physiology, medical and surgical ophthalmology, and blindness. Each question has a stem and five options, so that altogether there are 1000 individual questions and answers. The book is arranged so that questions appear on one page and answers on the following page. In many instances only an indication of whether the statement was true or false is given, but for about half of the questions a brief explanatory note is included to indicate why the answer should be true or false.

The book is intended for undergraduate use, but the standard is probably a little high for the average undergraduate, and the book might be of use to the postgraduate starting ophthalmology. For the undergrate to read through the questions and answers would certainly be educative, and I am sure would prove helpful in preparation for an MCQ examination in ophthalmology.

The authors have successfully avoided ambiguity in the questions, though here and there, for example in the first question, the common mistake of having options which are not completely independent of each other occurs. This is, however, a minor criticism of a useful booklet which is good value at the price.

WALLACE S FOULDS

**World Blindness and its Prevention.** Vol 3. Edited by International Agency for the Prevention of Blindness under the direction of Carl Kupfer. Pp 183. £22.50. Oxford University. Press: Oxford, 1988.

This book gives a summary of the Third General Assembly of the International Agency for Prevention of Blindness held in New Delhi 1986. It looks back to what has been achieved over the previous decade in the prevention of blindness while stressing the challenge of the future, with an estimated 30 million people in the world suffering from blindness, of which 80% is avoidable.

The main blinding diseases, cataract, trachoma, onchocerciasis, and xerophthalmia, are discussed and further attention is paid to the particular issue of cataract blindness and the need to mobilise manpower and resources to deal with this problem. There is a useful section on the activities of the IAPB in different parts of the world, as well as a chapter summarising the work of the World Health Organisation and non-governmental organisations.

This book draws attention to the problem of world blindness in brief and easily readable form. It will be useful reading for all ophthalmologists concerned with blindness throughout the world, as well as being valuable to health policy makers, public health specialists, and managers involved in community health.

A FOSTER

**Retinal Detachment Surgery.** 2nd Edn. By AH Chignell. Pp 162. £39.50. Springer-Verlag: London, 1988.

In the second edition of his excellent book on the surgery of retinal detachment Mr Chignell expands on the original theme of the first edition in presenting a personal account of an approach to retinal detachment surgery. His target is the general ophthalmologist who is engaged in anterior segment and other ophthalmic practice and who is called upon to do retinal detachment surgery from time to time. Since this represents the vast majority of those who carry out this kind of surgery on a worldwide basis the book fulfils its purpose admirably.

The chapters are logically arranged. Chapter 1 covers pathogenesis, presentation, and methods of examination. Succeeding chapters cover preoperative examination, management, and planning, then surgical detail, and finally postoperative management, complications, and failure.

By far the largest are the chapters on preoperative examination and preparation. There is reference to more complex problems, but quite rightly there is no description of vitrectomy technique, implying that this area is for the vitreoretinal specialist. For the same reason Mr Chignell may be forgiven for giving two lines only to a mention of silicone oil. The interesting flow chart for the treatment of proliferative vitreoretinopathy emphasises the role of vitrectomy in the treatment of all stages of this complication under certain conditions but does not recognise the use of silicone in the treatment of late stage disease in the hands of very many vitreoretinal surgeons throughout the world.

The text reveals that Mr Chignell has spent many years working with retinal detachment, and all that is written is based on sound working practices. The general ophthalmologist will find much that is of practical value on every page of this book, and this should help greatly in avoiding the problems which, as the preface to the second edition points, out, may lead to simple cases being turned into difficult ones as a result of faulty primary technique.

This book is not intended to be a comprehensive treatise on the many ways in which retinal detachment might be treated. The enthusiastic retinal specialist might wish to see mention of such things as Lincoff balloons or of pneumatic retinopexy. However, these methods have little place in the context of retinal detachment treated by general ophthalmic surgeons, and the text concentrates on basic sound technique which should avoid complication and failure and improve results.

The book is extensively illustrated by line drawings, photographs and by the legendary fundus paintings of Terry Tarrant. The references are mostly ones which go back some years, a fact that indicates how little has been written of any practical value on the subject of retinal detachment in more recent times. Mr Chignell's new edition of his book fills a very large gap in our literature and should be found on the operating table as well as the preoperative consulting room of all general ophthalmic surgeons who set out to treat a case of retinal detachment no matter how simple it may at first appear.

JOHN SCOTT

**Physiological Aspects of Clinical Neuro-Ophthalmology.** Eds C Kennard, F Clifford Rose. Pp 482. £35. Chapman and Hall: London, 1988.

Regular symposium attenders will be familiar with the two major problems (apart from speakers failing to turn up) inherent in the format. The first is the variability in content, interest, and presentation between speakers, and the second is the tendency to repetition, especially when the subject is relatively small print to start with. Neither of these problems has been wholly avoided in the book resulting from the meeting in July 1986 on physiological aspects of clinical neuro-ophthalmology. There are 42 contributors, about ¾ from Europe and the remainder from the USA. The idea was to allow a discussion of areas of common interest between neuroscientists, responsible for an ever expanding volume of research into the visual system, and neurologists and ophthalmologists trying to assimilate this information into clinical practice.

The book is divided into two major sections on the visual pathways and oculor motor system, with smaller sections on the pupil, fundus, and optic nerve. Over half the chapters are from basic scientists, and among the clinicians there are only a handful of ophthalmologists. The two major sections are the most successful, though both suffer from repetition. There are excellent chapters on psychophysical testing of visual function, the optic chiasm, and the fascinating phenomenon of 'blind sight' or residual vision following lesions of the retrogeniculate pathways. Both the scientists and clinicians come out well in the section on the oculomotor system. As an abstractor on this subject for *Ophthalmic Literature* I am sometimes driven to distraction by the literary incompetence of the oculomotor physiologists, and it is a relief to read a clear, concise and jargon-free paper such as Dr Keller's on cerebellar involvement in smooth pursuit eye movements. Guntrum Kommerell provides a stimulating chapter on oculomotor phenomenoma in infantile strabismus, proper recognition that this mysterious condition is of neuro-ophthalmic concern.

The sections on the pupil and fundus and the optic nerve I found less satisfying. There is, however, an admirably clear and succinct chapter on the pathogenesis of optic disc oedema from Professor Hayreh and a stimulating contribution from Iain McDonald.

The authors assembled a formidable cast for their symposium and on the whole they have been well served in the resulting book. I would recommend it as an excellent update on the subject, and a valuable source of reference for further reading.

JOHN S ELSTON

**Statistics with Confidence: Confidence Intervals and Statistical Guidelines.** By Martin J Gardner and Douglas G Altman. Pp 140. £7.95. British Medical Journal: London. 1989.

A number of medical journals and in particular the *BMJ* are laying increasing emphasis on the expression of confidence intervals as a means of indicating the importance to be attached to the numerical values of results, rather than the simple expression of a significance test based on the null hypothesis. This book arises from a collection of articles in the *BMJ* outlining the methods of calculating confidence intervals in a large number of situations, including some non-parametric statistics. A certain basic knowledge of statistics is necessary, but the calculations are set out as simply as possible and, used with care, should be accessible to most research workers. The orientation is primarily towards clinical research. A later chapter gives succinct guide lines on the correct use of statistics, making it clear that an understanding of statistical pinciples is essential. Consultation with a statistician is essential in planning a stage of any complicated project, to ensure that data collection has been valid when the stage of statistical analysis is reached.

The book suffers from certain defect inherent in any text derived from a series of sel contained articles. In spite of some connectin paragraphs there is an uncomfortable feeling o discontinuity. That said, it can be widel recommended to all but the most accomplishe statisticians, as it contains many methods o handling data with the aim of obtainin confidence intervals, which are not found i the short and more readable texts in commo use. It will prove invaluable to all currentl engaged in clinical investigation and treatmen trials.

D W HIL

**Ocular Pathology: A Colour Atlas.** By Myro Yanoff and Ben S Fine. Pp 248. £50. Gower London, 1988.

This book is a well illustrated synopsis of ocula pathology which serves as an introductory tex and as an atlas to accompany a more detaile textbook. It should be of value to candidate studying for the diploma in ophthalmology o the College of Ophthalmology examination and it is competitively priced. The book is ope to criticism in that there is no attempt t differentiate between the common and rar entities, and the bibliography is in parts dated Otherwise it is a pleasure to recommend thi colourful and attractive book.

WILLIAM R LE

**Ophthalmic Surgical Procedures.** By Peter Hersh. Pp 416. £45. Churchill Livingstone Edingburgh, 1989.

This book is intended as a speedy referenc covering common ophthalmic procedures an giving step by step instructions. It reflect accurately techniques as practised in the Unite States, and its references are limited almos entirely to United States sources. Very wid spacing round text and illustrations is intende to allow annotation and updating by the reader It is a useful summary and tabulated guide fo the ophthalmic surgeon, but does no encompass orbital surgery.

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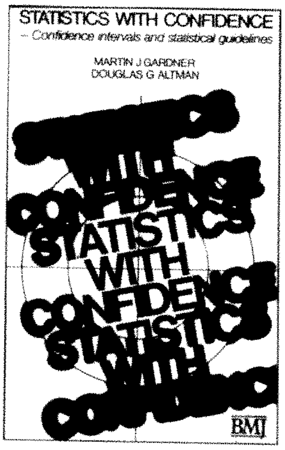
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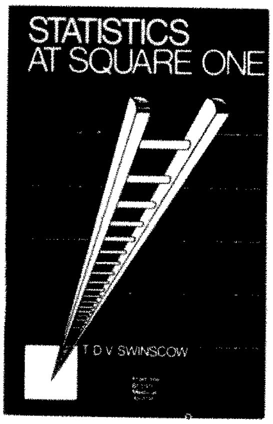

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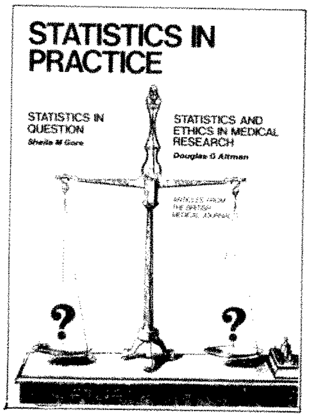

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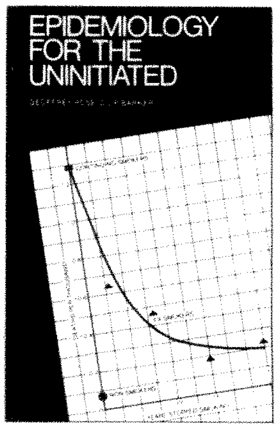

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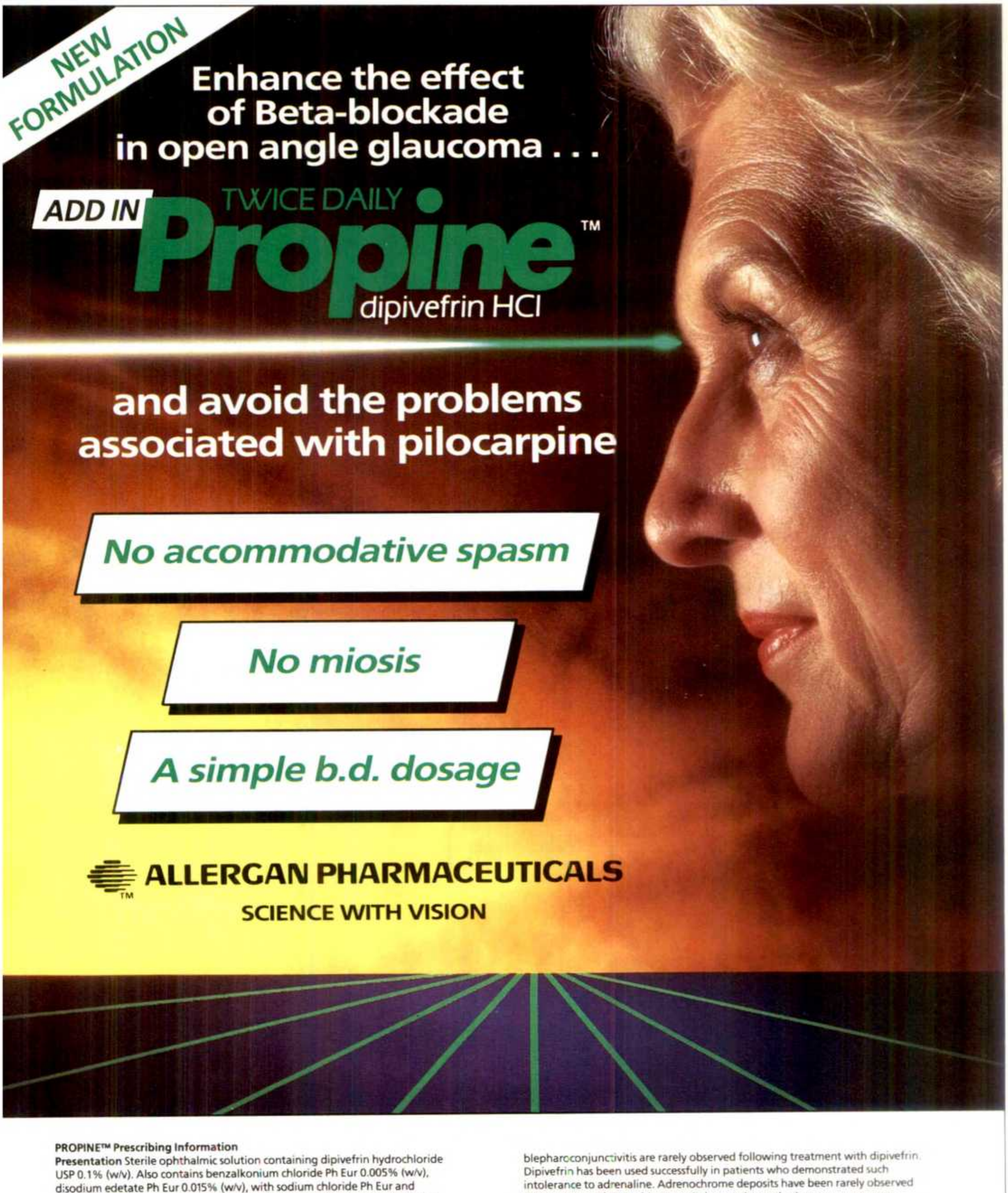

**PROPINE™ Prescribing Information**
**Presentation** Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** For the control of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* patients suffering from closed angle glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin during pregnancy has not been substantiated. *Precautions:* dipivefrin should be used with caution in patients with narrow angles since dilation of the pupil may trigger an attack of angle closure glaucoma. Macular oedema is a rare occurrence with adrenaline use in aphakic patients. Prompt reversal generally follows discontinuance of the drug. Macular oedema with dipivefrin does present as a possibility in the aphakic patient. *Adverse reactions:* rebound vasodilation and allergic blepharoconjunctivitis are rarely observed following treatment with dipivefrin. Dipivefrin has been used successfully in patients who demonstrated such intolerance to adrenaline. Adrenochrome deposits have been rarely observed following use of dipivefrin. Very slight transitory stinging may occur upon instillation in some patients. This product contains benzalkonium chloride and should not be used by patients continuing to wear soft (hydrophilic) contact lenses. **Pharmaceutical precautions** Store at room temperature. Discard any unused contents 28 days after opening the bottle. **Legal category** POM.
**Package quantities** Plastic dropper bottle containing 10ml.
**Further information** Nil. **Basic NHS Cost:** (as at October 1988) £4.65.
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Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

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'Timoptol' may cause side effects of systemic beta-blockade.

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Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

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Do not use in patients with soft contact lenses. Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

*Children:* Not recommended. Data not available for use in children.

*Nursing:* Mother should either stop nursing or stop 'Timoptol'.

*Pregnancy:* Not studied; weigh benefit against possible hazards.

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Hypersensitivity, rash, and urticaria.

Reactions with an unestablished relationship are ACMO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

BASIC NHS COST

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0.5% Ophthalmic Solution 'Timoptol', £5.82 per 5 ml pack.

PRODUCT LICENCE NUMBERS

0.25% Ophthalmic Solution 'Timoptol', 0025/0134. 0.5% Ophthalmic Solution 'Timoptol', 0025/0135.

Issued July 1989.

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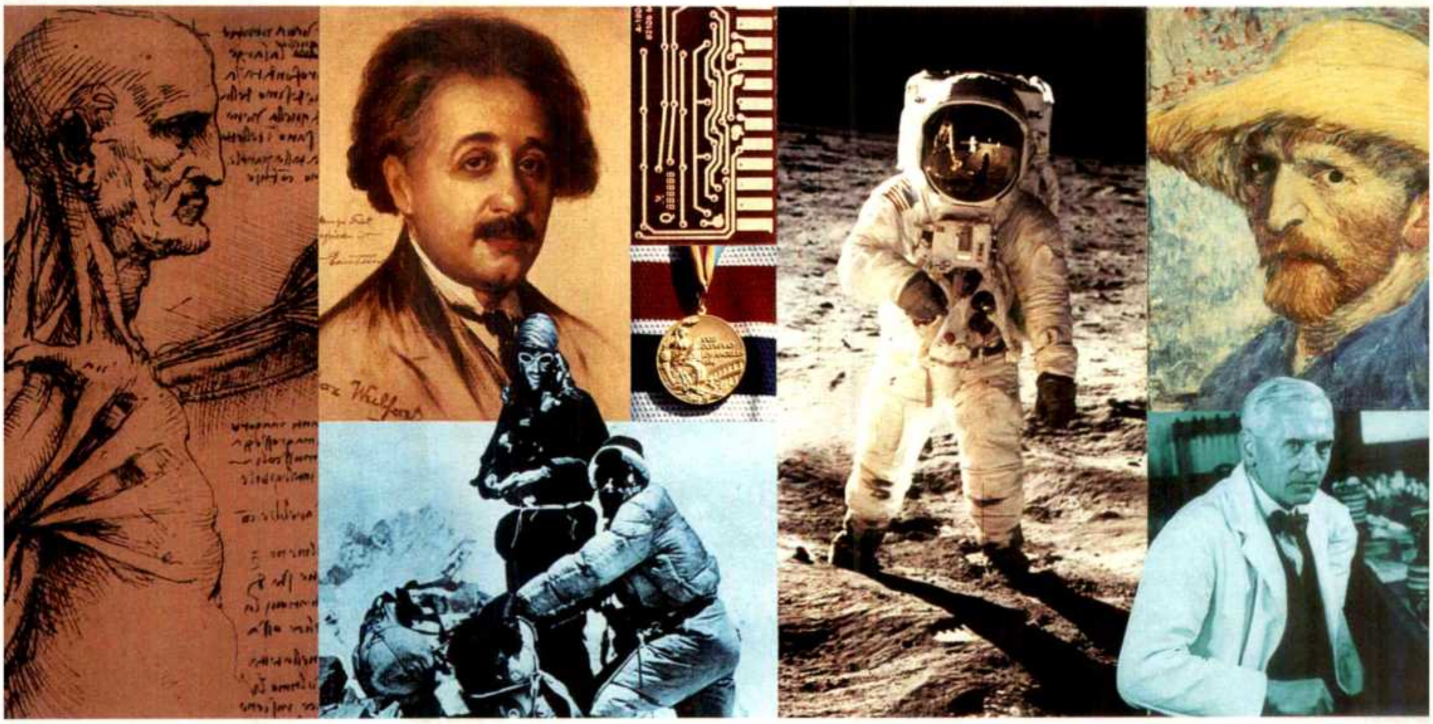

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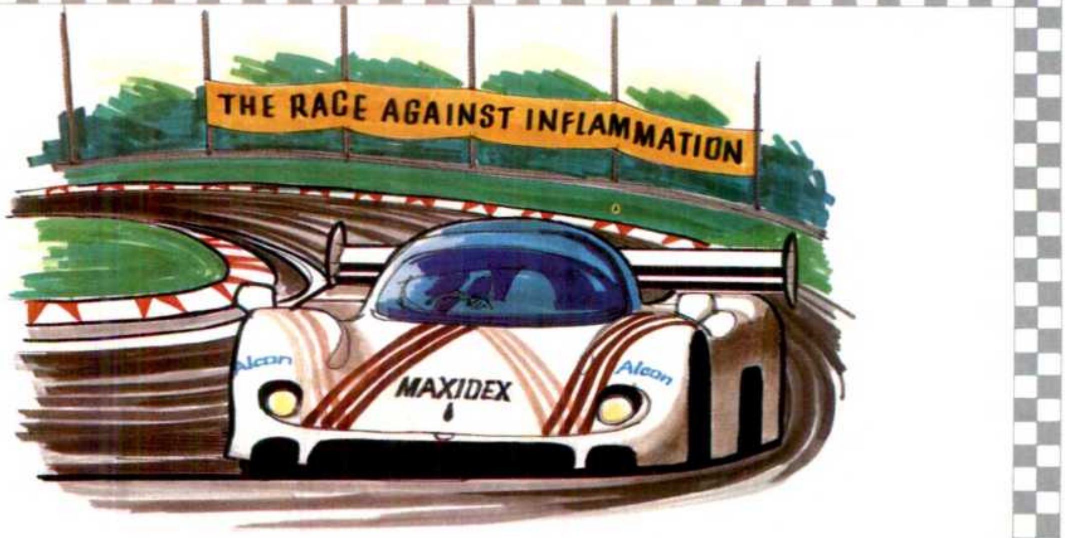

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REFERENCE:1. Watson, D. et al.: Penetration of Topically Applied Dexamethasone Alcohol into Human Aqueous Humor, Arch Ophthalmol 106: 686 687, 1988.

**PRODUCT INFORMATION: Presentation:** Dexamethasone PhEur 0.1% in a sterile, isotonic, ophthalmic suspension preserved with Benzalkonium Chloride BP 0.01%. **Uses:** Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **Dosage and administration:** One or two drops topically in the conjunctival sac(s) four to six times daily. In severe disease, drops may be used hourly. **Contra-indications:** Epithelial herpes simplex (dendritic keratitis), vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; tuberculosis of the eye; and in those persons who have shown hypersensitivity to any component of this preparation. **Warnings:** Use in the treatment of herpes simplex requires great caution. Not effective in the treatment of Sjorgen's keratoconjunctivitis. Infection appears to be enhanced with the presence of steroids. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. It is advisable that the intraocular pressure be checked frequently. This product contains benzalkonium chloride and should not be used when soft contact lenses are being worn. **Adverse reactions:** Glaucoma with optic nerve damage, visual acuity and field defects; cataract formation; secondary ocular infection following suppression of host response; and perforation of the globe may occur. **Pregnancy warning:** Although topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long-term treatment of pregnant patients. **Legal category:** POM. **Package quantities:** 5 ml and 10 ml. **P.L.:** 0649/5914.

*British Journal of Ophthalmology*, 1990, 74, 129–132

BRITISH JOURNAL OF
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## *Editorials*

# Contamination of contact lens storage cases

*Acanthamoeba* is a free living protozoan that causes a rare but devastating corneal infection. The disease has emerged, principally among contact lens wearers in recent years. Although by far the largest number of cases have been reported from the USA,[1] increasing numbers are also being seen in the UK.[2] The disease is possibly rarer, underdiagnosed, or underreported in Europe.[3]

The epidemiology is important because of the large numbers of lens users exposed to the risk of this potentially avoidable infection. It has been proposed that the recent increase in cases in the USA partly results from the growth in popularity of wearing contact lenses.[1] *Acanthamoeba* is found in air, soil, and in salt, fresh, and chlorinated water and can be commonly isolated in nasopharyngeal cultures of human upper respiratory tract infections.[4] *Acanthamoeba* keratitis has been shown in the USA to be associated with the use of home made saline solutions and swimming in contact lenses.[5] As for bacterial keratitis in contact lens users,[6] it has been shown that the solutions and containers for the care of lenses may be the source of the infecting organism.[7] The majority of cases reported have been in users of soft lenses, though the disease is also found in association with the wearing of hard lenses.[8]

Previous studies of asymptomatic wearers of contact lenses have shown *Acanthamoeba* present in home made saline but not in lens cases.[5,9] Larkin *et al*, in their paper on the contamination of contact lens storage cases in this issue, have now shown that *Acanthamoeba* may be present in a high proportion of these in asymptomatic users of contact lenses. This difference may be related to improved culture success. Their finding parallels the situation for bacterial contamination of lens cases, which occurs in 35–52% of asymptomatic subjects.[9] It has been expected because of the ubiquitous distribution of *Acanthamoeba*, the lack of effect of most cold lens disinfection systems against it,[10] and the probability that the presence of bacteria enhances its survival and growth.[7] Although the domestic water supply may be a source of this contamination, it remains only one of many potential sources of this widely distributed organism.[4]

The link between contamination of lens care material and infection has established one of the risks for keratitis in contact lens users. Others are only now being established for bacterial keratitis. The factors influencing the adherence of organisms to a lens surface are complex[11] and may or may not influence the spectrum of bacteria causing keratitis and their prevalence in users of different types of lenses.[12,13] The relative risks of ulcerative keratitis in contact lens wearers have recently been shown to be up to 15 times higher for extended wear soft lenses than for daily wear soft lenses.[14] It remains to be shown whether such considerations may also be important in *Acanthamoeba* infection.

These investigations have only just begun to unravel the pathogenesis and epidemiology of keratitis in contact lens users and many problems remain unsolved. The apparently higher incidence of amoebic keratitis in the USA might be explained by epidemiological comparisons with Europe, where lens use and hygiene practices, such as the use of home-made salines, may be different. The failure to link contaminated material for contact lens care with some cases of bacterial keratitis has not been explained.[15] A recent case report on a user of disposable soft lenses has shown that this may also occur in *Acanthamoeba* keratitis.[16] The reduced risk associated with hard lens wear, which Larkin *et al* have shown to be associated with a significantly increased rate of contamination of lens cases is also unexplained, and the risk of keratitis in rigid lens users has not yet been established. The problem of contamination by *Acanthamoeba* of material for the care of contact lenses is compounded by doubt about the efficacy of many cold disinfection systems against it.[10] However, it is of equal concern that the same solutions meet rigorous standards of efficacy against bacteria in the laboratory but have been shown repeatedly to fail in use. Although this may be partly for reasons of poor compliance by the patient, it is possible that the failure may be due to the development of a bacterial biofilm that has been found on the surfaces of contaminated lenses in vitro.[17,18] This is likely also to be important in container contamination and may have a role in resistance to disinfectants.

In order to create a safer environment for the contact lens user more needs to be known about both the epidemiology and the pathogenesis of lens related disease. This will be a continued challenge to the contact lens industry, regulatory bodies, and practitioners while contact lenses remain in widespread use.

JOHN DART

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# Albinism and anatomy

The average clinician going about his or her daily work may not have the time or the inclination to search for rational explanations for many phenomena the exact mechanisms of which are not apparent but which tend to be taken for granted. Examples of the sort of thing I mean would be ocular dominance, retinal rivalry, stereopsis, diplopia and confusion, and why convergent squints seem to cause amblyopia more often than divergent squints.

I have now discovered another riddle, and I am ashamed to have to admit that I did not know of its existence until I read the article in this month's issue by Russell-Eggitt and colleagues. It appears that albinos have an anomalous chiasmal crossing arrangement, something I expect every ophthalmologist knows except me. Having heard of this anatomical oddity for the first time, I was prompted to wonder what lay behind it. At first sight it appears to be just an associated condition without any obvious causal relationship. This starts to seem unlikely, however, when we learn that all albinos have the anomaly; surely it must be very closely related to the albinotic state.

Digressing for a moment, may I remind readers of the discoveries of the last few years concerning the laying down of the visual pathways during postnatal development? The general principle which has been established is that the development of the intracerebral visual pathways depends to some extent on the input of appropriate stimuli. We have been told, for example, how the anatomy of the lateral geniculate body can vary according to whether or not occlusion has been applied to one eye in experimental animals, and the same sort of thing has been suggested in the occipital cortex.

The situation in albinism, as explained and illustrated in the current article, is that in the central 20° of the field in one eye, retina stimulated by light coming from the opposite side, which would normally be expected to project to the ipsilateral cortex, does not do so but projects back to the opposite side. (I prefer to talk about the 'opposite side' rather than the 'nasal side' because it has more meaning in the context of what comes next.) I found this revelation profoundly disturbing for the following reason. I have always thought (and taught) that everything we 'relate to' (to use a bit of slightly unpalatable but I hope in this case appropriate jargon) on one side of our world is processed on the other side of our brain. This shows itself in many ways, not least in a variety of forms when hemicranial dysfunction occurs for one reason or another. The simplest example is in the unawareness of loss in many patients with homonymous hemianopia. It is not that they cannot see on one side, but that one side from a visual point of view has ceased to exist; they cannot even think about it.

This strict concept of 'side' implies a changeover point where right gives way to left at the centre. There is probably a small area at the centre which the brain recognises as centre and where the concept of one or other side does not operate. Such is probably true of the most basic of bodily functions, eating, excreting, and reproducing. We can probably add central vision as the fourth 'centralised' function. It is possible that, whereas the right and left sides are mediated by the opposite sides of the brain, central functions are bilaterally represented (sparing of the macula might be an example of this). Perhaps therefore the peculiar chiasmal arrangements of the albino are not so difficult to understand after all. Because their central vision is poor from an early age they may have developed a much less concentrated version of the 'centre'. Putting it another way, we may say they may have an extended central zone where right and left are not perceived as such but are dissolved into a large (20°) blurred centre. If this were to be the case I should expect a wide central area to be bilaterally represented in the cortex, and this might account for the anomalous decussation found in albinos. It would be interesting to have the views of an expert on this speculative explanation.

REDMOND SMITH

# Cataract surgery

There seems little doubt of the success of modern cataract surgery. The widespread acceptance of extracapsular surgery and the routine placement of a posterior chamber intraocular lens is encouraged by many reports and papers recording final acuity levels of 6/12 or better for over 80% of patients. For many individual surgeons this figure rises to over 90%.

We can now use such figures with confidence when discussing likely outcomes of projected procedures with our patients and, hopefully, with a clear conscience.

It may therefore come as a surprise to learn how much of our vaunted success is dependent on factors over which we have little influence but take for granted. In Britain at least our patients are still reasonably compliant. What the doctor says tends to go. It does not occur to us that patients will fail to attend for postoperative follow-up appointments, fail to use the prescribed drops, or decline to be tested for or wear necessary spectacles.

In this issue a paper by Dr Al Faran reports the results of modern cataract surgery undertaken at the King Khaled Eye Hospital in Riyadh. The study was made because the staff at the hospital considered that their results were not matching those achieved elsewhere. They report, for instance, final acuities of 6/12 (20/40) or better in 37% of patients, with commensurate figures for those seeing less well. The major responsible factor is the patients' failure to attend for refraction or to wear a spectacle correction. In many parts of the Islamic world and elsewhere the wearing of glasses is equated with blindness and can constitute a serious social stigma. The recorded acuities above are mostly uncorrected and are probably no worse than those achieved in many Western 'centres of excellence', where, as in Riyadh, many contributing surgeons are at various stages of their surgical training. Imperfect techniques and inexperience are bound to be associated with a higher rate of operative misadventure and a wider margin for error with preoperative biometry.

We all have our own favourite parameters for assessing the results of anterior segment surgical procedures. Two valuable ones are the postoperative incidence of retinal detachment and bullous oedema of the cornea. Al Faran reports a detachment rate of 1% and no cases of persistent corneal oedema. Admittedly the follow-up time (mean of nine months only) is far too short to be dogmatic, but one sees nothing here to suggest that the surgeons involved have cause for reproof. A 6·4% rate of vitreous loss following capsular rupture is what one might expect from a surgical team including those in training, while transient postoperative oedema in as few as 4·5% has to be regarded as excellent and unlikely to be followed by significant numbers suffering late decompensation.

Al Faran's problems are related to factors beyond his control. The high incidence of endemic sight-impairing disease, particularly trachoma and climatic droplet keratopathy (25% in this study), are gradually being overcome with improvements in community health. In my experience droplet keratopathy is more prevalent in the poorer strata of Middle Eastern society and often superimposed on preexisting corneal scarring, due either to trachoma or smallpox. The elimination of these conditions should therefore be followed by a similar fall in the incidence of droplet keratopathy.

The problems concerned with the refusal of large sections of a community to wear glasses where these are indicated are likely to respond only to the influence of effective universal education, and in Saudi Arabia will take one or two generations. The same applies to the reported sex differences in the patients of this study. The older age groups contain fewer females despite the higher incidence of cataract in Saudi women. For the age groups under 50 the sexes are equally represented, which hopefully indicates already some modification of traditional social behaviour. In time, therefore, Al Faran or his successors will be able to serve a population who will not only be more prepared to report their difficulties but also more inclined to keep their postoperative appointments!

Overseas students in London have frequently complained (to me) that sophisticated surgical techniques which have so dramatically altered patients' expectations have no relevance to the developing world. Poorer conditions called for inferior methods – intracapsular extraction and the Graefe knife. Dr Al Faran has demonstrated how wrong this is. How much worse off his patients would have been had they not had the benefit of excellent modern management. Other surgeons of whom we hear, working under even worse constraints, both physical and cultural, struggle to follow the precepts of their teachers and to maintain the highest possible standards. They must be given every possible encouragement to persevere.

ARTHUR STEELE

# Histogenesis of retinoblastoma

More than a century of controversy has surrounded the cell of origin of retinoblastoma. At the outset Virchow described the tumour as a glioma in the belief that it arose from the glial cells of the retina.[1] Subsequently, in a report of a single case, Flexner was the first to describe the rosettes which may be present in retinoblastomas and to designate this tumour a neuroepithelioma.[2] Later still Wintersteiner described rosettes in a series of cases and substituted the term neuroepithelioma for glioma, whether or not rosetting was present.[3] Both authors regarded rosettes as an attempt to form photoreceptors, leading Verhoeff to suggest the description 'retinoblastoma' in order to indicate the origin of all histological variants of the tumour from embryonic retinal cells and to parallel the name 'neuroblastoma.'

The term retinoblastoma was adopted by the American Ophthalmological Society in 1926.[4] In the same year Bailey and Cushing produced a classification of brain tumours based on histogenesis.[5] The medullary epithelium lining the embryonic neural tube differentiates into three groups of cells: the neuroblastic series which gives rise to neurons, the spongioblastic series which forms the glia, and the medulloblastic series of cells which are primitive and undifferentiated and which may lead to either glia or neurons. Using gold and silver stains they classified each tumour according to the type of cell predominating. Several attempts were made to apply the same principles to retinoblastoma.[6-10] Using silver impregnated preparations, Muñoz-Urra identified spongioblasts as well as astroblasts and astrocytes in the histogenesis of retinoblastoma.[6]

Parkhill and Benedict could not demonstrate any cell processes or fibrils indicative either of glia or of neurons using special stains and regarded the cells they saw as primitive and undifferentiated.[7] They postulated that the tumour was derived by dedifferentiation of normal astrocytes or Müller cells rather than from primitive precursors. They argued that the rosettes in retinoblastoma represented an attempt to reproduce the primitive epithelium of ependymal cells in the embryonic neural tube. Similar rosettes are seen in ependymomas. Because of this, and in accord with the wide acceptance of the term glioma for all brain tumours of neuroectodermal origin, they chose to revert to the glioma description for the retinal tumour, subclassifying the neoplasms as of retinoblastoma type when the cells were undifferentiated like those of neuroblastomas or medulloblastomas, of neuroepithelioma type when partial differentiation was indicated by rosette formation like that of primitive spongioblastic cells, and of astrocytoma type in the rare examples when the tumour cells were nearly as well differentiated as normal astrocytes.

On similar principles, Broders graded retinoblastomas from I for true gliomas composed of more or less mature astrocytes to IV for the majority of retinoblastomas with no cellular differentiation.[11 13] Grinker was in agreement with his predecessors that the presence of rosettes was indicative of an origin from primitive rods and cones, and he retained the term neuroepithelioma for tumours with this feature. However, he considered that tumours without rosettes arose from primitive retinal epithelial cells capable either of neuroepithelial differentiation to neurons or of spongioblastic differentiation to glia.[8]

More recently, using histochemical stains and electron microscopy, Tso *et al* found that the cells of rosettes have morphological features in common with photoreceptor cells,[14 15] while Sang and Albert demonstrated uptake of catecholamine precursors in retinoblastoma cell cultures suggestive of the production by the tumour of similar neural transmitters to those found in normal retina.[16] Synaptic vesicles may be seen in retinoblastomas with photoreceptor differentiation. Retinoblastoma cells have been shown to have features in common with embryonic retina. For example, the oncogene N-*myc* is expressed in retinoblastoma tumours and in fetal retina but not in adult retina.[17] Biochemical studies have demonstrated the ability of retinoblastoma cells to synthesise substances present in normal maturing and adult photoreceptors such as binding proteins for retinol and retinoic acid.[18-21] Tissue culture experiments have shown that the differentiation of retinoblastoma cells may be modulated by chemical substances.[22 23] Both glial and neuronal differentiation have been observed.[24 25] The expression of retinol and retinoic acid binding proteins is a sign of differentiation[26] and proliferation of retinoblastoma cells,[27] and those of other tumours which contain these binding proteins[28] may be inhibited by retinoids. Immunohistochemical studies performed with antibodies to substances specific to the retina, including retinal S-antigen,[29-32] S-100 protein,[33] neuronal markers such as neuron specific enolase,[24 31 33-35] and glial markers such as glial fibrillary acidic protein[24 31 33 35-38] have indicated both a neuronal and a glial origin for retinoblastoma.

In their article in the present issue of the *BJO* Tarlton and Easty have further explored the immunohistological reactivity of retinoblastoma using a panel of monoclonal antibodies to achieve a more specific immunolocalisation. Their data suggest that the tumour arises from an early multipotential cell with the capacity to develop into an inner or outer retinal cell so that the resultant tumour cell population is heterogeneous.

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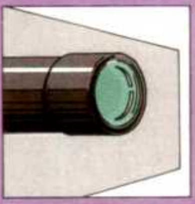

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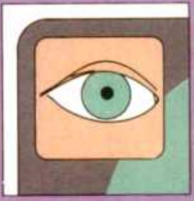

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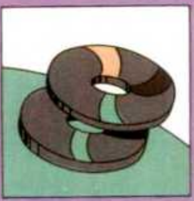

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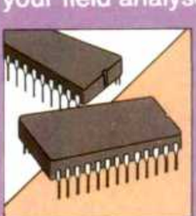

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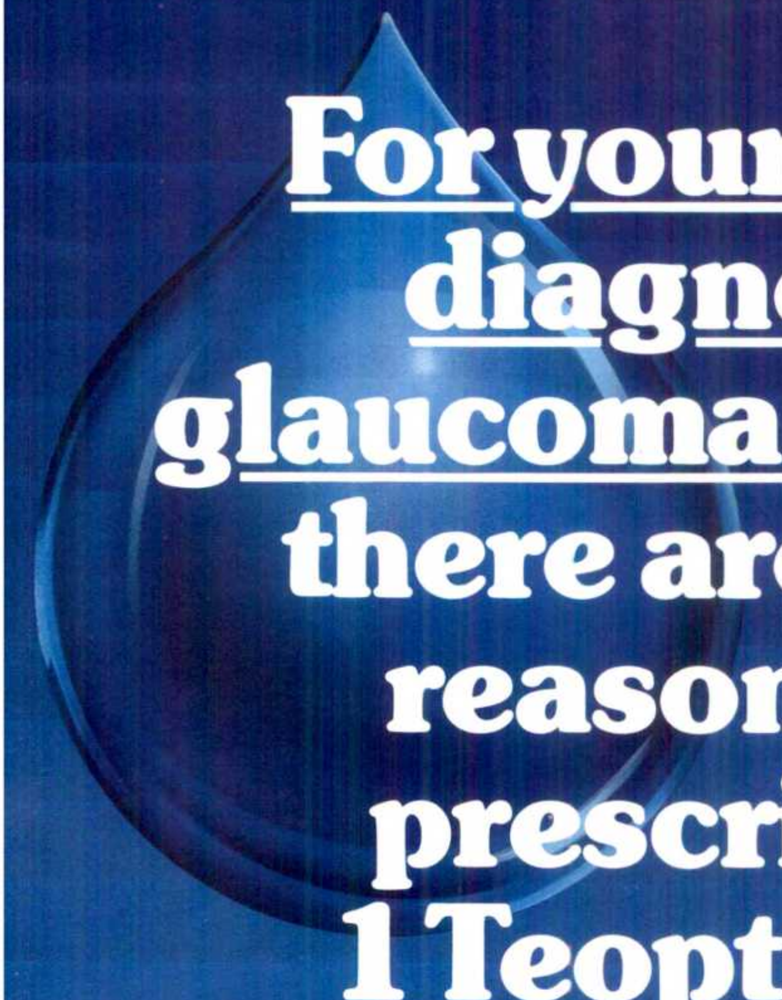

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ORIGINAL ARTICLES

# Contamination of contact lens storage cases by *Acanthamoeba* and bacteria

D F P Larkin, S Kilvington, D L Easty

**Abstract**

**In order to identify possible risk factors for microbial keratitis the storage cases for contact lenses of 102 asymptomatic lens wearers were tested for contamination by bacteria and free-living amoebae. Of this group 43 had significant counts of viable bacteria and only 40 had negligible counts. Seven had contamination by acanthamoebae, of whom six also had significant bacterial counts. These results were categorised according to the type of contact lens worn and the lens disinfection method. The high rates of contamination by apathogenic and pathogenic organisms, in particular *Acanthamoeba*, and the probable support by contaminating bacteria of *Acanthamoeba*, are discussed.**

Contact lenses have become an increasingly popular mode of correction of refractive errors, and it is estimated that there are now 1·5 million lens wearers in the United Kingdom (G Jones, Association of Contact Lens Manufacturers, personal communication, 1989). Sight-threatening corneal infection by bacteria[1] or *Acanthamoeba*[2,3] is the most important complication of contact lens wear. Microbial contamination of the storage case is the usual source of infecting organisms.[4] Soft lens wearers are at greater risk of these infections, probably on account of enhanced microbial adherence to the lens material.[5,6] A previous survey by Donzis *et al*[7] of the cases of 100 asymptomatic lens wearers found that 46% were contaminated by bacteria and no cases by *Acanthamoeba* (although 'home-made' saline bottles of two patients were).

A study of the efficacy of lens disinfection was undertaken in which contamination of lens storage cases by bacteria and free-living amoebae (FLA) was ascertained. The study group of 102 included wearers of hard and soft lenses who used a variety of disinfection methods. Particular attention was given to *Acanthamoeba*, because there has been an exponential increase in incidence of reported *Acanthamoeba* keratitis in recent years.[3] This increase is primarily due to infection in contact lens wearers, and among lens wearers those that use home-prepared saline are recognised to be at highest risk.[3,8]

TABLE I *Contamination of hard and soft lens systems*

| *Lens type* | *No.* | *TVBC <10/ml* | *TVBC >$10^4$/ml* | *Acanthamoeba contam.* | *Other FLA contam.* |
|---|---|---|---|---|---|
| Hard | 35 | 6 | 22 | 1 | – |
| Soft | 67 | 34 | 21 | 6 | 2 |
| Total | 102 | 40 | 43 | 7 | 2 |

The table shows numbers of patients with lens case contamination by bacteria, *Acanthamoeba*, and other free-living amoebae (FLA) categorised according to type of contact lens worn. For the purpose of statistical analysis a total viable bacterial count (TVBC) of <10/ml is considered negligible, and >$10^4$/ml is considered significant. Note: the other FLA were one isolate each of *Vahlkamphia* and *Hartmannella*.

## Patients and methods

### PATIENTS

One hundred and two patients were recruited. They had been wearing daily-wear lenses for at least six months, were cosmetic lens wearers (using lenses only for correction of minor refractive errors), and had no eye disease. All patients were asymptomatic and were recruited from optometry practices at the time of scheduled review visits. Patients were instructed to bring their lens storage cases and disinfecting solutions, but were not informed about the contamination survey. Participating patients' storage cases were exchanged for new cases. The following information was recorded: lens type, lens disinfecting regimen used, and whether saline solutions were home prepared.

### LABORATORY METHODS

Cases were shaken and opened under aseptic conditions. All solution was transferred to a sterile universal container. A sterile cotton-wool swab moistened with sterile unpreserved saline was then rubbed over the internal surface of the case and the tip added to the universal container. The contents of the container were then mixed in a vortex mixer for 10 seconds, and divided for bacterial and amoebal studies.

*Bacterial isolation.* Solution was diluted 1:10 into a disinfectant neutraliser and left to stand for 10 minutes. The medium used was that of Norton *et al*[9] modified here by the inclusion of 0·4 g/l of beef liver catalase for peroxide and sodium thiosulphate 20 g/l for chlorine. 10 μL aliquots of the neutralised sample were cultured on blood agar and on cysteine, lactose, electrolyte-deficient (CLED) plates. After incubation for two days the isolates showing colony morphology typical of *Serratia* and all non-lactose-fermenting organisms were subcultured and identified by the API 20E system

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(API Laboratory Products, Basingstoke).

Total viable bacterial counts (TVBC) were made by the pour-plate method using yeast extract agar.[10] Serial 10-fold dilutions to $10^{-6}$ were made in 1/4 strength Ringer's solution. Plates were incubated in air at 30°C for three days. A total viable count of $>10^6$/ml was considered significant for the purpose of analysis.

*Amoebal isolation.* Remaining storage case solution in the universal which had been vortexed was centrifuged at 2000 *g* for 10 minutes. The supernatant was aspirated and the pellet resuspended in 100 $\mu$l of neutraliser. Previous studies have shown that the neutraliser is not inhibitory to *Acanthamoeba* trophozoites or cysts (data not shown). This was inoculated on non-nutrient agar seeded with *Escherichia coli*[11] and incubated at 30°C. Plates were examined daily by low power microscopy for seven days. Amoebae were characterised to genus level according to cyst and trophozoite morphology.[11]

Pathogenicity of *Acanthamoeba* isolates was tested on African green monkey kidney (Vero) cell cultures.[12] Cell monolayers were inoculated with amoebae, incubated at 32°C, and examined daily for cytopathic effect.

## Results

A total of 102 lens wearers participated in the study, 45 male and 57 female. The age range of the patients was 17–73 (mean 32) years. Of these, 35 (34·2%) wore hard or rigid gas-permeable lenses and 67 (65·7%) wore soft lenses. Eighty-two patients used chemical disinfectants, 19 used heat methods, and one used home-prepared saline solution without any recognised disinfecting regimen. In addition to the latter patient four prepared their own saline solution for rinsing after disinfection.

Of the total, the storage case solution of 43 (42%) patients had TVBC/ml of $>10^6$ and 40 had TVBC/ml $<10$. Nineteen had TVBC/ml between 10 and $10^6$. The culture results for the two lens types are shown in Table I. The association between hard lens wear and significant bacterial contamination was statistically significant ($\chi^2=9{\cdot}38$; df=1; $p<0{\cdot}05$).

Culture results according to disinfectant method used are shown in Table II. The association of significant bacterial contamination with chlorhexidine was statistically significant ($\chi^2=5{\cdot}3$; df=1; $p<0{\cdot}05$). This association was not statistically significant for any other disinfection method.

TABLE II *Contamination associated with different lens disinfection systems*

| *Disinfecting method* | *No.* | *TVBC <10/ml* | *TVBC >10⁶/ml* | *Acanthamoeba contam.* | *Other FLA contam.* |
|---|---|---|---|---|---|
| Chlorhexidine | 35 | 10 | 20 | – | 1 |
| Hydrogen peroxide | 20 | 9 | 3 | – | 1 |
| Heat | 19 | 13 | 4 | 3 | – |
| Chlorine based | 9 | 1 | 6 | 2 | – |
| Other chemical | 18 | 7 | 9 | 1 | – |
| None* | 1 | – | 1 | 1 | – |

The table shows numbers of patients with lens case contamination by bacteria, *Acanthamoeba*, and other free-living amoebae (FLA) categorised according to contact lens disinfection method.
*Home prepared saline but no recognised disinfectant method used.

A mixed growth was cultured from most contaminated lens cases. The majority of bacteria were environmental 'pseudomonads', being non-lactose-fermenting, oxidase-positive, Gram-negative bacilli. One recognised corneal pathogen, *Serratia marcescens* was isolated from 11 cases. Chlorhexidine was the disinfectant used by 10 of these patients and this association was significant (Fisher's exact test; 2-sided; $p=0{\cdot}04$). *Serratia liquifaciens* was isolated from 10 cases. Other lactose-fermenting organisms isolated include *Acinetobacter spp*, *Klebsiella spp*, *Enterobacter spp*, and *Aeromonas spp*. *Pseudomonas aeruginosa* was not isolated from any lens case.

Nine patients (8·8%) had case contamination by free-living amoebae; seven of these were *Acanthamoeba*, one *Vahlkamphia*, and one *Hartmannella vermiformis*. Of the seven patients with *Acanthamoeba* contamination six were soft lens wearers, six had significant numbers of contaminating bacteria, and six used commercially manufactured disinfecting solutions as instructed. *Acanthamoeba* was isolated from the case of one of the five patients who prepared saline solution at home: this was the patient who used no disinfectant. All patients were asymptomatic.

All seven *Acanthamoeba* isolates were cytopathic to Vero cells, producing complete destruction of the cell monolayer in 2–3 days.

## Discussion

We identified a disturbingly high incidence of storage case contamination by bacteria, in accordance with the report of Donzis *et al.*[7] We found that contamination by *Serratea marcescens*, a recognised corneal pathogen,[13] was significantly associated with chlorhexidine disinfection. *S. marcescens* infection due to contamination of chlorhexidine hand washing solution has been reported,[14] and R plasmids probably transfer resistance in a resistant strain.[15] However, we found contamination in the cases of patients using all disinfection methods and solutions. Similar bacteria contaminated hard and soft lens cases. The lower rate of bacterial contamination in soft lens cases reflects the use of hydrogen peroxide or heat disinfection by 38 patients in this group, these methods being more effective in reducing bacterial contamination (see Table II).[13]

It is even more disturbing that *Acanthamoeba* contamination of lens storage cases is more prevalent than expected. Numerically significant bacterial contamination has been found to coexist in most instances. This suggests that bacteria may support *Acanthamoeba* and possibly enhance virulence. Six of the seven patients from whose cases *Acanthamoeba* was isolated complied with lens hygiene instructions; only one patient prepared 'home-made' saline solutions, a widely recognised risk factor for *Acanthamoeba* keratitis.

This study indicates that *Acanthamoeba* contamination of lens storage cases must be far more common than *Acanthamoeba* keratitis. Keratitis probably arises in only a small proportion of those asymptomatic patients with lens case contamination, and the predisposing factors for development of keratitis have yet to be established.

Tap water rinsing of lenses prior to wear is widely advised by contact lens practitioners. A variety of free-living amoebae, including *Acanthamoeba*, can be isolated from domestic tap water samples (unpublished observations), and tap water might therefore be a source of contact lens case contamination.

It is established that most disinfecting methods are effective against bacteria and *Acanthamoeba* in the laboratory[16]; home disinfection does not reflect this in the majority of lens wearers. All must be aware of possible contamination by dangerous pathogens, and lens disinfectant manufacturers must develop new compounds that kill *Acanthamoeba* cysts. We suggest that tap water rinsing of lenses be strongly discouraged. We further suggest that inexpensive disposable lens storage cases be developed for use and disposal after two weeks. This would reduce the contaminant bacterial population and in some cases abolish *Acanthamoeba* contamination.

We thank Michael Killpartrick and Marcella McParland, optometrists, for kindly allowing us to survey their patients. This survey was supported in part by the British Council for Prevention of Blindness, Alcon Laboratories Ltd, and the South Western Regional Health Authority.

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# Albinism in childhood: a flash VEP and ERG study

Isabelle Russell-Eggitt, A Kriss, D S I Taylor

**Abstract**

**Flash visual evoked potentials (F.VEPs) and electroretinograms (ERGs) were recorded in a total of 20 young children with albinism (age range 5 months to 11 years, mean 4 years). All recordings were made without sedation. There were 13 oculocutaneous cases (one with Hermansky-Pudlak syndrome) and seven ocular albinos. Monocular flash stimulation commonly elicited an asymmetrical occipital VEP distribution with a well lateralised component at around 80 ms which was of opposite polarity in a comparison of VEPs from each eye. None of the normally pigmented matched controls or obligate female carriers showed this anomalous distribution. The albino electroretinogram, compared with controls, recorded under fully darkened conditions had a significantly larger a wave and significantly shorter latencies for both a and b waves. The accentuated ERG and asymmetrical VEP recorded in infants and young children with albinism permits distinction of these patients from those with congenital cone dysfunction and idiopathic nystagmus, with whom they may be confused by a clinical examination only.**

Albinism is a genetically determined heterogeneous group of disorders involving deficiency of the enzyme tyrosinase, which mediates conversion of tyrosine to the pigment melanin.[1,2] At least 10 forms of albinism have been described.[3-5] The commonest are autosomal recessive oculocutaneous albinism, in which skin, hair, and eyes are conspicuously involved, and X-linked ocular albinism, in which the hypopigmentation predominantly involves the eye.[6] Various non-allelic forms of oculocutaneous albinism occur. The children of two parents with different forms of albinism are likely to be normally pigmented.[7] 'Ocular' albinism does not solely affect the eyes; there is also less evident pigment dilution of skin and hair. If parents have dark brown hair with olive skin, the ocular albino child may have light brown hair that darkens slightly with age and fair skin that tans. The skin in ocular albinism and also in heterozygotes contains abnormal giant melanosomes,[8-10] but this feature is not unique to albinism.[11,12]

The degree of ocular hypopigmentation in albinism varies.[3] The irides are usually translucent[4]; this condition may be gross, especially in oculocutaneous albinism, when the lack of uveal pigment gives a 'pink eyed' appearance. In ocular albinism the irides may be brown, though usually the mid stroma transilluminates. Patients may be photophobic, but this is not a constant feature. The fundus is hypopigmented, with conspicuous large choroidal vessels. There may be a marked reduction of vessels forming the perimacular arcades.[13] The foveal region is not formed[14] and the optic disc may be hypoplastic.[13]

Female heterozygotes display a mosaic fundal appearance with small patches of hypopigmentation intermixed with pigmented areas.[15] However, the fundal picture varies, and both obligate heterozygotes without fundus changes[9,16] and female heterozygotes who are as severely affected as male offspring[17] have been reported. This variation in expression can be explained by the Lyonisation effect.[18]

Visual acuity and contrast sensitivity are usually reduced in all forms of albinism.[19,20] Both myopic and hypermetropic refractive errors are common.[21] Furthermore, there is a high incidence of squint and nystagmus.[21,22] The nystagmus is usually pendular and horizontal, but there may be a rotary component, and it may become jerky on lateral gaze.[23] The nystagmus often dampens when close vision is being used and, conversely, becomes more marked in bright illumination, with resultant reduction in vision.[23] The intensity of the nystagmus often lessens with age, and this may be associated with improvement in visual performance.[23]

All albino mammals appear to have anomalous projection of fibres in both the visual[20,24-34] and auditory modalities[35,36] (Fig 1). In the normally pigmented person fibres derived from the nasal half of the retina of each eye decussate at the chiasm, while temporal retinal fibres are uncrossed and project to the ipsilateral hemisphere. In albinos the majority of temporal retina fibres subserving the nasal field (from fixation to

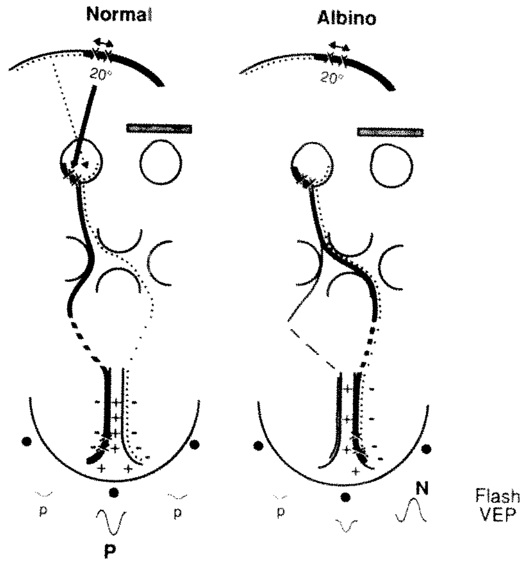

*Figure 1: Diagram of visual pathway from one eye in a normal control and an albino. In the albino, temporal retinal fibres subserving the nasal field from the fixation point to an eccentricity of 20° project anomalously to the contralateral hemisphere.*

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TABLE I *Hair colour may indicate tyrosinse activity in the oculocutaneous albinos (o-c). An improvement in visual behaviour, 'delayed visual maturation' (DVM), was noted in eight cases (asterisks). The most recent visual acuity is recorded in Snellen or in cycles/degree for the acuity card procedure. Central figures are for binocular acuities. H-P is the Hermansky-Pudlak case*

| | | | | | *Acuity* | |
|---|---|---|---|---|---|---|
| *Patient* | *Age at electrodiagnosis* | *Diagnosis* | *Hair colour* | *DVM* | *Right* | *Left* |
| 1 | 9 mo | o-c | Golden | * | | |
| 2 | 10 mo | o-c | White | | | |
| 3 | 5 yr | o-c | White | * | 4/60 | 4/36 |
| 4 | 9 yr | o-c | White | | 6/60 | 6/60 |
| 5 | 7 yr | o-c | White | | 6/18 | 6/60 |
| 6 | 18 mo | o-c | White | * | 3 cy/d | |
| 7 | 2 yr | o-c | White | * | 4/24 | |
| 8 | 7 mo | o-c | White | * | | |
| 9 | 5 mo | o-c | Golden | * | | |
| 10 | 5 yr | o-c | Golden | | 6/60 | 5/60 |
| 11 | 8 yr | o-c | Golden | | 6/36 | 6/18 |
| 12 | 7 mo | o-c | White | | | |
| 13 | 4 yr | H-P | Golden brown | | 6/24 | 6/24 |
| 14 | 7 mo | Ocular | Golden | * | 4 cy/d (15/12) | |
| 15 | 7 yr | Ocular | Brown | | 6/60 | 6/24 |
| 16 | 9 yr | Ocular | Light brown | | 5/60 | 5/60 |
| 17 | 6 yr | Ocular | Light brown | | 6/60 | 6/60 |
| 18 | 9 yr | Ocular | Brown | | 6/24 | 6/24 |
| 19 | 11 yr | Ocular | Brown | | 6/36 | 6/60 |
| 20 | 8 mo | Ocular | Golden | * | 6/18 | |

an eccentricity of about 20°), anomalously cross with the nasal retinal fibres (Fig 1). Monocular visual evoked potentials (VEPs) to flash are reported to have a contralateral emphasis in 70% of adult albinos,[25] though no detailed specification of components was made. This VEP effect most probably reflects the abnormal fibre projection pattern in albinism.

All adult albinos are reported to have an abnormal contralateral emphasis for pattern onset reponses,[30] but the same group of workers found only 33% of albino children appear to have similar abnormalities.[33]

Boylan[32] recorded flash VEPs in three young infants (aged 1, 4·5, and 7 months) and reported a predominant late positivity (150–316 ms) on the side of scalp contralateral to the eye stimulated.[32] Recently Guo *et al*[37] recorded from 19 albino patients aged between 1·5 and 20 years and found that in 88% of patients the flash VEP main positivity on the ipsilateral side of the scalp was significantly delayed and in 59% of patients this component was attenuated.

This paper describes consistent ERG differences in young albino children compared with controls, and specific flash VEP changes at a latency of about 80 ms, not reported before. Our technique demonstrates a very high detection rate and is relatively easy to perform in infants. This specific pattern of abnormality found in albinism allows ready distinction from other conditions, such as cone dysfunction and idiopathic nystagmus, with which it may easily be confused on purely clinical grounds.

## Patients and methods

A series of 20 albino patients – 13 oculocutaneous (one Hermansky-Pudlak) and seven ocular albinos – were clinically examined. Visual acuity testing (with the acuity card procedure in the preverbal), slit-lamp examination of iris translucency, cycloplegic retinoscopy, and fundus examination (where possible including photography) were all carried out. Immediate relatives were also examined when they were available. A full history was taken, with special emphasis on ocular details.

Electrophysiological recordings were obtained without pupil dilatation, and none of the patients was sedated. Recordings were also made on three carrier mothers; two of them were recorded with undilated pupils. In one carrier only one of the pupils was dilated (Fig 2).

The age range of the albino patients was 5 months to 11 years; the group mean was 4·3 years (SD 3·5). Recordings from the patients were compared with those of normally pigmented matched controls of similar age (mean age 5 years, SD 3·14).

Silver/silver chloride EEG electrodes were attached to the lower eyelid, within 1 cm of the eyelid margin, and across the posterior scalp. Occipital electrodes were placed at $O_Z$ [(10–20 system), approximately 3 cm above the inion] and at approximately 4 cm either side of $O_Z$ (20% of the ear to ear distance through $O_Z$). The eye and occipital electrodes were all referred to a common mid-frontal reference ($F_Z$; 10–20 system). The clinical neurophysiology convention of 'negative upwards' was used to display the VEP. For consistency, ERG traces were displayed by this convention also.

A Grass photic stimulator (Model PS22, intensity setting 4, $4 \cdot 75 \times 10^6$ lumens) was used to present flash stimuli at 3/s under fully darkened conditions. The recording amplifier bandpass was 3–125 Hz, and 128 responses were averaged for each run. The sweep duration was 300 ms, which included a 15 ms prestimulus interval.

Flash VEPs were recorded in all 20 patients. ERG recordings were obtained in 16 patients. Four of the younger patients would not accept electrodes under their eyes.

## Results

The ocular findings and general pigmentation of subjects are summarised in Table I. The mothers and other immediate female relatives of three male cases with ocular albinism did not show a mosaic fundus pattern. In these cases, therefore, it was not possible to distinguish between an autosomal recessive and an X-linked inheritance pattern. One patient was atypical in that he also had bilateral partial iris colobomata inferiorly and had developed posterior subcapsular cataracts requiring lensectomy at age 6 years.

Less than half of the patients with oculocutaneous and ocular albinism (8/20) had very poor purposive visual behaviour for the first 2–3 months after birth. Vision then gradually improved, though eventual acuity levels never approached normal levels.

Figure 2 shows the flash ERG and VEP traces of two patients with oculocutaneous albinism (left side), and those of a patient with X-linked ocular albinism and his mother's (obligate carrier) (right side). All three albino patients had a conspicuous VEP asymmetry. On each side of the midline (arrowed) there were components of opposite polarity which showed an apparent polarity inversion when responses were compared from each eye (crossed asymmetry). In contrast, VEPs from the carrier (lower right traces) had normal features. They were symmet-

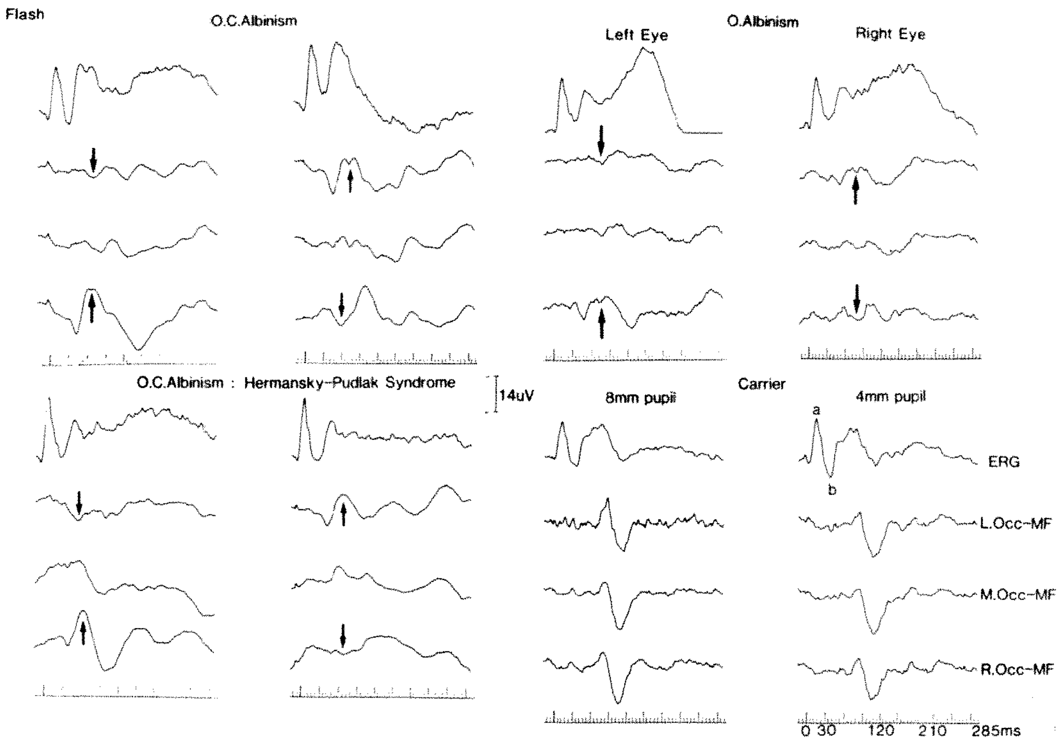

*Figure 2: Retinal and occipital responses in cases with albinism (oculocutaneous – upper left, ocular – upper right, Hermansky-Pudlak – lower left) and in a female carrier (mother of the albino case – lower right). Note the accentuated a wave in ERG and marked VEP asymmetry in all albino cases, but not in the female carrier.*

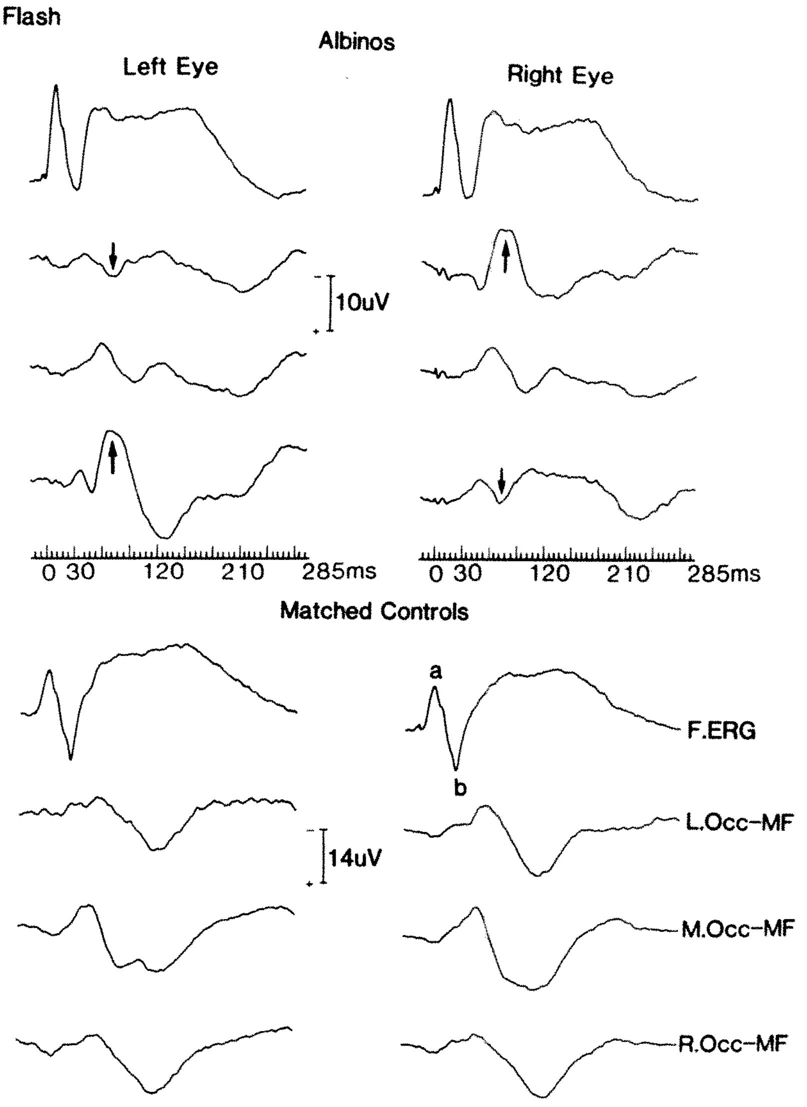

*Figure 3: Group average ERGs and VEPs for albino patients (upper traces), and matched controls (lower traces). Note accentuated ERG a wave and VEP crossed asymmetry in albino recordings.*

rical about the midline and were similar for the two eyes.

All 20 albino patients showed similar crossed asymmetry features, which were most conspicuous and consistent at a latency around 80 ms.

Figure 3 shows the group average ERGs and VEPs for the albino patients (upper traces) and for matched controls (lower traces). Note the marked VEP asymmetry in the albino group, which is best seen on each side of the midline at around 80 ms. For left eye stimulation a prominent negativity is recorded over the right occipital scalp (contralateral N80-C.N80), and a smaller component at the same latency is present at the left occipital electrode (ipsilateral P80-I.P80). For right eye stimulation the distribution is reversed, with a negativity over the left occipital area (C.N80) and a positivity over the right (I.P80). The contralateral N80 is followed by a larger positivity of more variable form and latency (range 96–178 ms, mean 129·3 ms, SD 19·3, amplitude 16·0 µV, SD 5·5; C.P130).

Tables II and III summarise the amplitude and latency data for all albino patients. The mean and standard deviations of C.N80 and I.P80 for

TABLE II *Albino flash VEP. Mean latency (ms) and standard deviation for ipsilateral and contralateral component at 80 ms*

| | | *I.P80* | *C.N80* |
|---|---|---|---|
| Left eye: | Mean | 79·05 | 76·53 |
| | SD | 12·33 | 8·57 |
| Right eye: | Mean | 87·28 | 75·85 |
| | SD | 10·85 | 7·71 |

TABLE III *Albino flash VEP. Mean amplitude (µV) ipsilateral and contralateral components at 80 ms*

| | | *I.P80* | *C.N80* |
|---|---|---|---|
| Left eye: | Mean | 7·82 | 10·13 |
| | SD | 3·81 | 4·48 |
| Right eye: | Mean | 5·49 | 8·89 |
| | SD | 3·34 | 4·42 |

TABLE IV *Flash ERG latency (ms)*

| | | *Left eye* | | *Right eye* | |
|---|---|---|---|---|---|
| | | *a* | *b* | *a* | *b* |
| Albino patients | Mean | 14·55 | 36·08 | 14·58 | 35·63 |
| n=16 | SD | 0·86 | 3·14 | 0·6 | 3·53 |
| Controls | Mean | 15·65 | 39·15 | 16·13 | 39·53 |
| n=16 | SD | 1·61 | 1·06 | 1·81 | 1·48 |
| Significance | p | <0·02 | <0·01 | <0·01 | <0·01 |

TABLE V *Flash ERG amplitude (μV)*

| | | *Left eye* | | *Right eye* | |
|---|---|---|---|---|---|
| | | *a* | *b* | *a* | *b* |
| Albino patients | Mean | 16·97 | 21·6 | 17·94 | 21·91 |
| n=16 | SD | 6·45 | 11·91 | 7·45 | 13·47 |
| Controls | Mean | 11·62 | 28·12 | 12·29 | 28·35 |
| n=16 | SD | 4·63 | 8·03 | 4·04 | 7·77 |
| Significance | p | <0·01 | NS | <0·01 | NS |

the left and right eye stimulation are given. In general, the C.N80 component was the larger, more conspicuous component (mean amplitude 9·4 μV) and was detectable in 37 of 40 monocular records (93%). The ipsilateral component (I.P80) on average measured 6·6 μV and was present in 32 of the 40 monocular records (80%). Both C.N80 and I.P80 were together present in 30 of the 40 monocular records (75%).

There were no significant latency or amplitude differences when the same component was compared in the response from each eye. Both oculocutaneous and ocular albinos showed the crossed asymmetry features with equal clarity.

The flash VEP of controls had a different emphasis. The C.N80 and I.P80 components were not apparent in control recordings. Instead control subjects had a virtually symmetrical VEP distribution with a midline negativity, with a mean latency of 63 ms (SD 6·7) and amplitude of 8·7 μV (SD 5·6). This was followed by a conspicuous positivity peaking, on average, at 95 ms (SD 8·9) with an amplitude of 23·7 μV (SD 7·9).

The averaged flash ERGs of albinos showed statistically significant differences from those of normally pigmented controls of the same age (Tables IV and V). On average, the a wave was 40–50% larger in albinos ($p<0·01$). The mean b/a amplitude ratio for the albino ERGs was 1·26 (SD 0·39), and this was significantly different ($p<0·01$) from the ratio of 2·51 (SD 1·1) for the age matched control group. The a and b wave latencies were earlier in albinos than in controls by 1 and 3 ms respectively ($p<0·02$).

## Discussion

Our results agree with those of other studies showing that albinos have monocular flash VEPs which are prominent on the side of the scalp contralateral to the stimulated eye.[25 27 30 31 37] However, unlike those previous studies we report a consistent negative component at around 80 ms (C.N80) which is prominent on the side of the scalp contralateral to the stimulated eye and is usually, though not always, accompanied by a concurrent ipsilateral positivity (I.P80). Following the contralateral negativity (C.N80) there is a positivity of more variable latency and amplitude (C.P130).

This specific occipital asymmetry at around 80 ms was not observed in normally pigmented controls. The highly consistent latency relationship between I.P80 and C.N80 components strongly suggests a common generator with a dipole property. This explanation would be analogous to that used to account for the distribution of the somewhat later P100 component of the pattern reversal response to half field stimulation in normally pigmented control subjects.[38] However, the possibility of independent generators for C.N80 and I.P80 cannot be completely excluded, as occasionally only one of these lateralised components was recordable.

If the dipole hypothesis is invoked, then the waveform recorded in the midline is likely to represent a transitional waveform similar to that observed following half field pattern reversal stimulation in controls.[39] Thus, it is suggested that in the albino most fibres representing central areas of the visual field from one eye project to medial aspects of the contralateral occipital hemisphere. In the albino infant and young child, at least, activation of this area produces an early positivity at the cortical surface which is picked up by the ipsilateral electrode (I.P80). A coincident negativity is present at the deeper cortical layers, and this is best picked up by the contralateral electrode (C.N80). Presumably the C.N80 component tends to be larger than I.P80, as the contralateral scale electrodes are closer to the generator area than are ipsilateral scalp electrodes.

It is not clear at present why this activity at 80 ms is not apparent in the records of normal controls. One possibility is that in controls it is present but masked by activity arising from the cortical foveal representation, not present in albinos.

We recorded flash VEPs using a monopolar derivation widely spaced occipital electrodes, 4–5 cm from the midline, referred to a distant midfrontal electrode. Others have used a bipolar montage with occipital electrodes nearer to the midline (approximately 3 cm, at $O_1$ and $O_2$, of the 10-20 system) and used nearby ipsilateral references either at the ear[37] or at central scalp locations.[32] Such derivations are suboptimal, as they span the occipital areas over which VEP activity is prominent (see Kriss[40] for fuller discussion). The 80 ms component was of consistent latency when comparing individuals, and there was no evidence of ipsilateral or contralateral 'delays' reported by others.[32 37] We found that the C.N80 component was often followed by a somewhat variable positive component at 130 ms (C.P130). It is probably this contralateral component that some previous studies have reported on.[32]

Our ERG findings broadly agree with those of Krill and Lee,[41] who found, using the conventional corneal ERG, single flash technique, elicited under dark adapted conditions, that both oculocutaneous (five cases) and ocular albinos (three cases) had significantly larger a and b waves, and shorter latencies for these components compared with normally pigmented controls. Six carriers of the X-linked condition showed no difference compared with controls.

The ERG differences can most probably be ascribed to the stronger effects of the flash stimulus on the albino eye, owing to more light entering through the translucent iris, as well as greater fundal reflectance and light scatter because of lack of retinal pigment absorption. Similar a and b wave changes are recorded from the normally pigmented eye with very bright flashes. With increasing flash intensity the a wave progressively enlarges, but the b wave saturates and at very high intensities attenuates to a small extent.[42] The discrepancy between our study and that of Krill and Lee[41] for the b amplitude is most probably due to differences in the intensity of the flash stimulus (not specified by Krill and Lee).

It can sometimes be difficult, when relying soley on a clinical examination to be certain whether an infant with nystagmus has congenital cone dysfunction or ocular albinism. In both conditions photophobia may be prominent. In our experience the ERG and VEP findings in albinism are specific and are thus very useful in helping to make a differential diagnosis between these two conditions. Furthermore we find that the crossed asymmetry VEP pattern is not found in other conditions in which nystagmus is conspicuous, such as congenital motor nystagmus or latent nystagmus associated with dissociated vertical deviation.[43]

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# Visual outcome and complications after cataract extraction in Saudi Arabia

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## Abstract

**Cataract is the leading cause of blindness in Saudi Arabia. The author studied 1383 patients who had undergone cataract extraction (total of 1520 procedures) from October 1985 to March 1986 at the King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. All patients were observed for at least two months. Of 1520 eyes 555 (37%) achieved a visual acuity of 20/40 or better, 309 (20%) a visual acuity of 20/50–20/60 after surgery, and 656 (43%) eyes a visual acuity of 20/70 or less. The number of eyes that had intraoperative complications was 176 (12%). The number of eyes that had postoperative complications was 539 (35%). Some eyes had more than one complication. The main factors responsible for failure to achieve visual acuity of 20/40 or better were: (1) error of refraction in 492 (32%) eyes; (2) preexisting corneal scarring and opacity in 211 (14%) eyes; (3) climatic droplet keratopathy in 134 (9%); and (4) presumed visual loss due to glaucoma in 134 (9%) eyes.**

Cataracts are an enormous medical, financial, and social burden. Annually at least 300 000 to 400 000 new, visually disabling cataracts occur in the United States, and 5 to 10 million occur worldwide.[1] Throughout the world cataracts are most prevalent in areas where the amounts of annual and daily sunlight are high.[2,3] In Saudi Arabia cataract has been found to be the leading cause of blindness, accounting for 55% of all cases. Furthermore, it is the second most important cause of visual loss, accounting for 35·5%.[4] The visual outcome and complication rates are the objective means of assessing the success of cataract surgery.[5,6] While cataract surgery is considered to be safe and effective, irreversible blindness either from the complications of advanced, untreated cataract, or from the complications of surgery, may occur.[1] In addition associated ocular diseases increase the risk of complications and reduce the chance of a good visual outcome.[7]

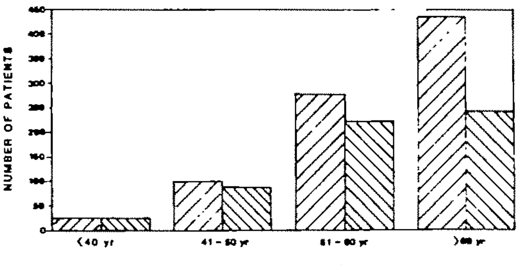

*Figure 1: Age and sex distribution of 1383 patients who underwent cataract extraction.*

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It has been noted that the number of cataract surgeries performed at the King Khaled Eye Specialist Hospital (KKESH) is large. It also has been thought that the visual outcome differed from that reported in western countries. It was therefore decided to study patients undergoing cataract extraction at KKESH. The major objectives of this study are: (1) to determine the visual outcome and the factors influencing visual outcome after cataract extraction and (2) to assess the complications of cataract extraction.

## Patients and methods

A total of 1520 consecutive (senile or presenile) cataract extractions from 1383 patients were analysed from October 1985 to March 1986 at the King Khaled Eye Specialist Hospital. This retrospective case review included patients aged 35 years or older.

### CLINICAL EXAMINATION AND FOLLOW-UP

A diagnosis of cataract was made after full ophthalmic examination, including biomicroscopy, tonometry, and indirect ophthalmoscopy. Ultrasonography was performed to assess the posterior segment of the eye if the media were opaque and for intraocular lens power calculation. After cataract surgery the patients were observed daily for two to three days in the hospital. After discharge from the hospital they were observed weekly for two weeks and then monthly for at least two months. Patients excluded from this study were those who gave a history of ocular trauma, were less than the age of 35 years, or who showed retinal detachment by ultrasonography. In addition patients who did not complete a follow-up for at least two months were excluded.

### SURGICAL PROCEDURES

All surgical procedures were performed by standard microsurgical techniques for cataract surgery, with or without intraocular lens implantation. There were 1469 (95%) extracapsular cataract extractions (ECCE) and 76 (5%) intracapsular cataract extractions (ICCE). A total of 144 (10%) eyes had other ocular procedures performed at the time of cataract extraction. Forty-three patients (3%) had trabeculectomy and 93 patients (6%) had anterior vitrectomy, because of the vitreous loss. Other procedures such as keratectomy for climatic droplet keratopathy and pterygium excision were performed in eight patients. The procedures were performed by several surgeons with various levels of experience.

## Results

Of the 1383 patients in this study 831 (60%) were male and 552 (40%) were female. The male to female ratio was 1·5:1 (Fig 1). Their ages ranged from 35 to 95 years, mean 64 years. The follow-up ranged from two months to 38 months, mean nine months, after date of surgery. The number of patients aged 40 or more years was 1337 (97%).

Table I shows the visual acuities before cataract surgery and the visual acuities achieved at least two months after cataract extraction in 1520 eyes. Of these, 555 (37%) eyes attained 20/40 or better and 309 (20%) eyes attained a visual acuity of 20/50–20/60; 455 (30%) eyes attained 20/70–20/200. Fifty (3%) eyes had a poor visual acuity of between 20/300 and 20/400, and 151 (10%) eyes had a visual acuity of between hand motion and light perception (HM–LP).

Seven hundred and fifteen eyes (47%) had complications. Some eyes had more than one complication.

*Intraoperative complications.* 176 eyes (11·6%) had intraoperative complications, which included vitreous loss in 97 (6·4%); rupture of the posterior capsule in 85 (5·6%); zonular dialysis in 23 (1·5%); significant bleeding in 22 (1·4%); Descemet's membrane detachment in 18 (1·2%); and other complications in 23 (1·5%) eyes (Table II).

*Postoperative complications.* 539 eyes (35·5%) had postoperative complications. These included posterior capsule opacity in 150 (9·9%) eyes; peaking pupil in 130 (8·6%); high intraocular pressure in 90 (5·9%); corneal oedema in 68 (4·5%); ruptured or loose suture in 47 (3·2%); and other complications in 62 (4·0%) eyes (Table III).

A total of 965 eyes (62%) did not achieve a visual acuity of 20/40 or better. Table IV shows the factors responsible for failure to achieve a visual acuity of 20/40 or better. It was found that 492 (32%) eyes did not have a final refraction. 211 eyes (14%) had corneal scarring and opacity; 162 (11%) had climatic droplet keratopathy; 134 (9%) had glaucoma with cupping of the disc, probably responsible for the level of visual acuity; 67 (4%) had posterior staphyloma and myopic retinal degeneration; 61 (4%) had diabetic retinopathy; and 51 (3%) had posterior capsular opacity. Non-myopic macular degeneration was found in 44 (3%) eyes, macular oedema in 21 (1%), retinal detachment in 14 (1%), optic atrophy in 16 (1%), amblyopia in 14 (1%), vitreous haemorrhage in 12 (1%), vitreous opacity in 11 (1%), and a few other rare factors.

TABLE I *Visual acuity before and after cataract extraction*

| | *Preop. VA* | | *Postop. VA* | |
|---|---|---|---|---|
| *Visual acuity* | *Number of eyes* | *(%)* | *Number of eyes* | *(%)* |
| 20/15–20/40 | 0 | (0) | 555 | (37) |
| 20/50–20/60 | 12 | (1) | 309 | (20) |
| 20/70–20/200 | 232 | (15) | 455 | (30) |
| 20/300–20/400 | 118 | (8) | 50 | (3) |
| CF-LP | 1158 | (76) | 151 | (10) |
| Total | 1520 | (100%) | 1520 | (100%) |

VA=visual acuity. CF=counting fingers. LP=light perception.

TABLE II *Intraoperative complications (176 eyes)**

| *Complications* | *Number* | *% (of 1520)* |
|---|---|---|
| Rupture of capsule | 85 | 5·6 |
| Vitreous loss | 97 | 6·4 |
| Zonule dialysis | 23 | 1·5 |
| Detachment of Descemet's membrane | 18 | 1·2 |
| Bleeding | 22 | 1·4 |
| Others: | 23 | 1·5 |
| Iris complication | 15 | 1·0 |
| AC collapse | 2 | 0·1 |
| Global perforation | 1 | 0·1 |
| Others | 5 | 0·3 |

*291 complications occurred in 176 eyes. AC=anterior chamber.

TABLE III *Postoperative complications (539 eyes)**

| *Complications* | *Number* | *% (of 1520)* |
|---|---|---|
| Wound leak | 12 | 0·8 |
| Iris prolapse | 9 | 0·6 |
| Peaking pupil | 130 | 8·6 |
| External infection | 16 | 1·0 |
| High IOP | 90 | 5·9 |
| Hyphaema | 32 | 2·1 |
| Retinal detachment | 7 | 0·5 |
| Ruptured/loose suture | 47 | 3·2 |
| Astigmatism | 36 | 2·4 |
| IOL displacement | 21 | 1·4 |
| Postcapsule opacity | 150 | 9·9 |
| Residual cortex | 50 | 3·2 |
| Corneal oedema | 68 | 4·5 |
| Others | 62 | 4·0 |

*730 complications occurred in 539 eyes.

TABLE IV *Factors adversely affecting visual acuity (>20/40 after cataract extraction)*

| *Complications* | *Number of eyes* | *% (of 1520)* |
|---|---|---|
| No final refraction | 492 | 32·4 |
| Corneal scar/opacity | 211 | 13·9 |
| Climatic droplet keratopathy | 162 | 10·6 |
| Glaucoma/cupped disc | 134 | 8·8 |
| Diabetic retinopathy | 61 | 4·0 |
| Post staphyloma/myopic retinal degeneration | 67 | 4·4 |
| Senile macular degeneration | 44 | 2·9 |
| Macular oedema | 21 | 1·4 |
| Retinal detachment | 14 | 0·9 |
| Optic atrophy | 16 | 1·0 |
| Amblyopia | 14 | 0·9 |
| Vitreous haemorrhage | 12 | 0·8 |
| Vitreous opacities | 11 | 0·7 |
| Others | 89 | 5·8 |

## Discussion

Eye disease, visual impairment, and blindness have long been recognised as major causes of human suffering and disability in the Kingdom of Saudi Arabia. The National Eye Survey conducted by the King Khaled Eye Specialist Hospital in 1984 revealed that 1·5% of the population in Saudi Arabia is blind by World Health Organisation (WHO) standards (less than 3/60 vision in the better eye with best available correction).[4] At the national level the leading causes of blindness are cataract, trachoma, refractive error, corneal scars, iatrogenic from medical or surgical treatment, and glaucoma.[4] The visual outcome after cataract extraction depends on several factors: corneal transparency, the status of the vitreous, and the functional integrity of both the retina and optic nerve.

The visual outcome in selected series of patients after senile cataract surgery is usually better than in unselected series of patients. Bernth-Petersen[6] reported visual acuity of 6/12 (20/40) or better in 81·6% of his selected series of patients with senile cataract after surgery. This is due to the avoidance of patients with pre-existing ocular diseases such as corneal opacity, optic atrophy, or retinal detachment. In our study it is interesting to note that 555 eyes (36%) achieved a visual acuity of 20/40 or better after cataract surgery, and only 864 eyes (56%) achieved a useful vision of 20/60 or better. This was due to many reasons, the first being that final refraction was not performed on 492 eyes (32%).

This points to a problem that may face ophthalmologists working in developing countries. Certainly it highlights a common clinical problem in Saudi Arabia, which is supported by the finding of the National Eye Survey, that the error of refraction was the first most common cause of visual loss in Saudi Arabia.[4] This dilemma might be attributed to the customs and cultural habits of the people in Saudi Arabia, where the majority are not accustomed to wearing glasses. Sometimes ophthalmologists do not determine their patients' refractive errors, nor do they prescribe corrective spectacles or lenses, believing that their patients will not use them.

The second reason is the corneal scarring and opacities from past inflammations and infections. These include trachoma, smallpox, and measles. In spite of the significant reduction of the prevalence of trachoma and the eradication of smallpox, these corneal opacities are the result of diseases acquired at an earlier time in the Kingdom's history, when medical care was not of today's high standards.

The third reason is climatic droplet keratopathy (CDK), which was found in 162 (11%) eyes. The presence of climatic droplet keratopathy, or spheroidal degeneration, involving the central cornea contributed significantly to the reduction of vision. Climatic droplet keratopathy is commoner in males than in females. In Saudi Arabia presumably males are more exposed to ultraviolet radiation than are females, who are usually protected by wearing veils, or by being outdoors less often than males.

It is interesting to note that the male to female ratio in our study is 1·5:1. This is contrary to the fact that cataract in our general population was found to be more common among females than in males.[4] However, this discrepancy may be explained by the fact that this is a hospital based study, and in this country males seek medical advice more than females, who do not drive and who generally stay at home.

Noteworthy is the high prevalence of cataract among patients under the age of 60 years. This might be explained by excessive exposure to sunlight. Ultraviolet light has been considered as a predisposing factor for cataract formation. This was confirmed by Collman and his coworkers.[8] They found an increased risk factor of cataract formation among dark eyed subjects, which is consistent with reports of high prevalence rates of cataract in areas populated with dark eyed persons who are exposed to sunlight.

Senile macular degeneration (SMD) is one of the main factors in the reduction of visual acuity after cataract surgery in western countries. This does not seem to be the case in developing countries. The prevalence of senile macular degeneration in the cataract population was 13·2% in one study.[6] Age related macular degeneration in our study was found only in 44 eyes (2·8%). This may mean a lower prevalence of senile macular degeneration than in America and Europe in the same age group of patients.

It is important to note that the majority (76%) of the eyes had a preoperative visual acuity of from counting fingers to light perception. These eyes had mature senile cataract and required prompt surgical intervention to prevent hypermature cataract and its unpleasant sequelae. Lack of visualisation of the posterior segment coupled with a poor history does not allow us to select patients free of preoperative ocular complications which later contribute to reduced visual acuity after cataract surgery. With the high number of cataract patients being treated, we expect to see patients with immature cataract, and we shall be able to identify many preoperative factors responsible for reduced visual acuity.

Correction of refractive error is a major challenge, and all efforts should be made to encourage people to use glasses. It is also important to recommend a routine use of the intraocular lens after cataract surgery whenever possible. As cataract is not only the leading cause of blindness in Saudi Arabia but also the second most important cause of overall visual loss, special care during and after operation is expected to decrease the visual loss due to cataract surgery. This special care is of paramount importance in a country where in the past an iatrogenic element was a considerable factor in blindness.[4]

Finally, this study points to a major clinical problem which needs an early solution to decrease the rate of blindness in Saudi Arabia. The backlog of blinding cataract cases should be given priority for surgery. It is expected that, once the cataract backlog is controlled, glaucoma may become the main cause of blindness. Public health education should be developed so that patients with visual loss know how to seek help. The eye departments at different hospitals in the Kingdom of Saudi Arabia should be upgraded and provided with proper facilities and enough qualified physicians appointed to perform effective and safe cataract surgery.

In conclusion, the proper evaluation of patients for cataract surgery and the complete visual rehabilitation of those patients are important in both the immediate and the long-term postoperative period. Failure of a cataract operation is not only a personal tragedy but also a major socioeconomic burden to the individual and to his society.

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# Immunohistological characterisation of retinoblastoma and related ocular tissue

John F Tarlton, David L Easty

**Abstract**

**The immunohistological reactivity of six retinoblastomas was investigated by means of 18 monoclonal antibodies and compared with that of adult and fetal retina. The antigenic profiles were found to be characteristic for each cell type studied and indicated that a panel of monoclonal antibodies could achieve a specific immunolocalisation not afforded by any single antibody. Immunohistological comparison between retinoblastoma and adult and fetal retinal cells provided evidence of the histogenesis of the tumour. The data suggest that the tumour arises from an early multipotential cell, which retains the capacity to develop differentiation characteristics associated with inner or outer retinal cell types, resulting in a heterogeneous tumour cell population. A cell with such differentiation potential predominates in the retina prior to the primitive neuroepithelial layer division at eight weeks' gestation.**

Retinoblastoma is the commonest ocular malignancy of newborn babies and infants. Despite advances in early diagnosis and treatment, the mortality rate due to metastatic spread remains above 15%. It is particularly high in parts of the world where there is a lack of immediate medical care. Although established therapeutic techniques are effective in dealing with most primary malignancies, it is the metastases that kill,[1] and further techniques must be investigated for their identification and treatment.

The clinical applications of monoclonal antibodies have been explored with regard to the diagnosis and treatment of neuroectodermally derived tumours.[1-11] A panel of monoclonal antibodies, tailored to the antigenic profile of the tumour, may be used to locate malignant cells in extraocular sites such as cerebrospinal fluid[10 12] and bone marrow,[8 13 14] and help to determine the extent of metastatic spread. In addition tumour-positive antibodies have potential value in immunotherapy and drug targeting to prevent the dissemination of tumour cells. Knowledge of the immunohistochemical reactivity of the tumour would also provide a useful adjunct to conventional histological classification and assist in assessing the prognosis.

In order to explore these and other potential uses of monoclonal antibodies comprehensive data on the immunochemical reactivity of the tumour are required, and antibodies must be assessed to determine their relative affinity for retinoblastoma and normal ocular tissue.

The histogenesis of retinoblastoma has been the subject of many recent investigations. Histological and microscopic studies have demonstrated characteristics associated with both astrocytic and photoreceptor cells,[15 16] and immunohistological investigations using antibodies against antigens associated with specific cell types, such as glial fibrillary acidic protein,[15 17-22] S-100,[20] retinal s-antigen,[15 23 24] and neuron specific enolase,[15 17 20 21 25] have indicated both neuronal and glial origin of retinoblastoma. Since such evidence remains inconclusive, an alternative approach to elucidate further the origin of the tumour is to compare its antigen expression with that of adult and fetal retinal cell types by means of a panel of monoclonal antibodies recognising a wide range of antigenic determinants. The retinoblastoma stem cell could then be classified according to the developmental lineage of retinal cells.

We report here an immunohistological study of six specimens of retinoblastoma using a panel of 18 monoclonal antibodies directed against antigens associated with neuroectodermal and epithelial tissue, as well as differentiation, oncofetal, and other antigens of mixed phenotypic distribution. Comparisons have been made with the reactions of fetal retinas of various ages and adult retina to provide evidence of the tumour origin.

## Materials and methods

### IMMUNOHISTOCHEMISTRY

Fresh operative samples of six well differentiated retinoblastomas, nine disease-free adult eyes, and 10 fetal eyes, ranging from 10 to 16 weeks' gestation, were snap frozen and stored in liquid nitrogen. Cryostat sections 5 μm thick were mounted on gelatin coated slides and air dried for 2 to 24 hours. Endogenous peroxidase activity was blocked by immersion in 2% hydrogen peroxide for 15 minutes, followed by two 5-minute phosphate buffered saline (PBS) washes, and the sections incubated for 15 minutes with 20% normal rabbit serum (Nordic) in PBS to block non-specific protein binding sites. Each subsequent incubation was followed by two 5-minute PBS washes. 50 μl of appropriate monoclonal antibody was added to each section for 60 minutes at room temperature in a humid chamber, followed by successive 15-minute incubations in secondary rabbit antimouse immunoglobulin (Dako, 1:20 in PBS) and tertiary mouse peroxidase antiperoxidase complex (Dako, 1:40 in PBS). The secondary and tertiary stages were repeated to amplify the binding. The sections were soaked in tris buffered saline (TBS, pH 7·6) for 5 minutes, and incubated with 4-chloro-1-naphthol (10 mg in 100 μl ethanol, added to 25 ml TBS containing

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TABLE I *Monoclonal antibody panel*

| *MAb* | *Immunogen* | *Antigen tissue distribution* |
|---|---|---|
| RT97 | Rat brain | 210K subunit neurofilament, neurones[28] |
| UJ181.4 | 16-Week human fetal brain | Fetal brain, neuroblastic tumours, PNT[29] |
| UJ127.11 | 16-Week human fetal brain | 220–240K glycoprotein, brain, neuroblastic tumours[30] |
| BF10 | Rat brain | 155K neurofilament, neurones[28] |
| A Thy-1 | Human Thy-1 antigen | 20K glycoprotein, neuroblastoma, glioma[31-34] |
| FD32.2 | Human glioma | |
| FD44 | Glioma tissue | Blood vessels[4] |
| P1153/3 | IMR6 NBL cell line | Neural type cells, neuroblastoma[6,13,35] |
| UJ13A | 16-Week human fetal brain | All neuroectodermal tissues and tumours[3] |
| A2B5 | Chick retinal cell culture | Gangliocide GQ, neuroectodermal tissue[6,36,37] |
| H11 | Muscle myoblast | Neuroectodermal tissue and tumours[38] |
| FD19 | Astrocytoma | GFAP 50K, glial tissue and tumours[6,39] |
| M148 | Medulloblastoma | 110–130Kd membrane glycoprotein, blood platelets |
| LE61 | Cytoskel. ext. epith. cells | 45K cytokeratin, simple epithelium, carcinomas[40] |
| 2.3F9 | Fibronectin | |
| MI/N1 | CHP100 NBL cell line | Some neural cells, granulocytes, neuroblastoma[30] |
| UJ167.11 | Fetal brain | Some neuroectoderm[14] |
| UJ308 | Fetal brain | Some neural cells, granulocytes |

50 µl 6% hydrogen peroxide, and left to allow precipitate to settle) for 30 minutes, giving a black reaction product where antibody binding has occurred. The sections were counterstained with eosin or alcian yellow, and mounted beneath coverslips in Aquamount aqueous mountant (Emscope).

The adult retina samples were stained with the panel of antibodies to establish the consistency of reactions, and thenceforth were placed on the same slide as the tumour and fetal tissue and stained simultaneously in subsequent assays, thereby standardising the results. The intensity and distribution of the staining was assessed microscopically, and a score between 0 (negative) and 9 (intense positive) attributed by comparison with the adult retinal tissue. The reactions were repeated a number of times to ensure consistency, and mean values were obtained. In each case adult and fetal ocular tissue acted as positive and negative controls; normal serum and antibody found to be consistently negative provided additional controls.

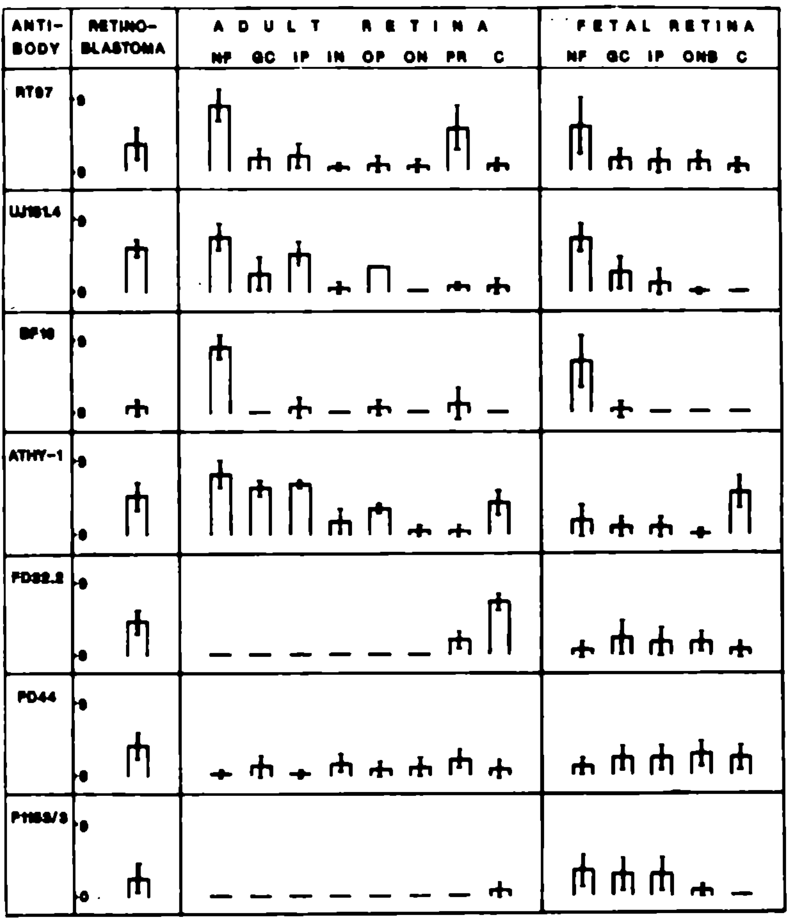

*Figure 1: Mean comparative staining intensities of reactions, scored 0 (negative) to 9 (intensely positive), for those antibodies demonstrating variation in tissue affinities. Mean values and standard deviations are shown. NF, nerve fibre layer; GC, ganglion cell layer; IP, inner plexiform layer; IN, inner nuclear layer; OP, outer plexiform layer; ON, outer nuclear layer; PR, photoreceptor layer; C choroid; ONB, outer neuroblastic layer.*

## MONOCLONAL ANTIBODIES

A panel of 18 monoclonal antibodies was selected for use in the study. These were raised by conventional hybridoma techniques[26,27] and are listed in Table I, along with their antigen tissue distribution where known, and reference to their origin.

## Results

A total of 29 examinations were conducted on the retinoblastoma samples and 22 on both the adult and fetal retinas, by means of the panel of monoclonal antibodies.

Each tumour sample displayed marked heterogeneity in its binding of some of the monoclonal antibodies (particularly ATHY-1, FD32.2, and FD44). In these cases the overall staining intensity was recorded:

Monoclonal antibodies UJ13A, A2B5, and H11 were strongly positive in all retinal tissues and retinoblastoma; M148 and FD19 were moderately positive in all tissues; and UJ127.11 showed identical distribution to UJ181.4. Antibodies found to be negative throughout were LE61, 2.3F9, UJ167.11, UJ308, and the MI/N1. The comparative antigen expressions for the other antibodies in the panel are shown in Figures 1 and 2, and examples of the immunohistological reactions are illustrated in Figures 3 and 4.

## ANTIBODY LOCALISATION

The reactions of antibodies which differentially marked the tissues assessed in this study, namely RT97, UJ181.4 (UJ127.11), BF10, A THY1, FD32.2, FD44, and P1153/3, are illustrated in Figure 1, and those of antibodies which showed variable affinities for fetal retinas of different ages are shown in Figure 2.

*RT97 (neurofilament antigen).* This cytoplasmic antigen was expressed in the nerve fibre layer after 12 weeks' gestation, and in mature photoreceptors. Retinoblastoma showed mild affinity for this antibody, though this was particularly sensitive to antibody titre.

*UJ181.4, UJ127.11 (neuroblastic antigens).* In all tissues characterised it was found that these cell surface antigens were expressed in parallel, remaining constant throughout development, and limited primarily to the inner retinal layers. Moderate to intense expression was seen in all the retinoblastomas.

*BF10 (neurofilament antigen).* This cytoplasmic antigen was limited in distribution to the nerve fibre layer of post 11-week retina.

*A THY-1 (human Thy-1 antigen).* There was found to be moderate to intense marking of the

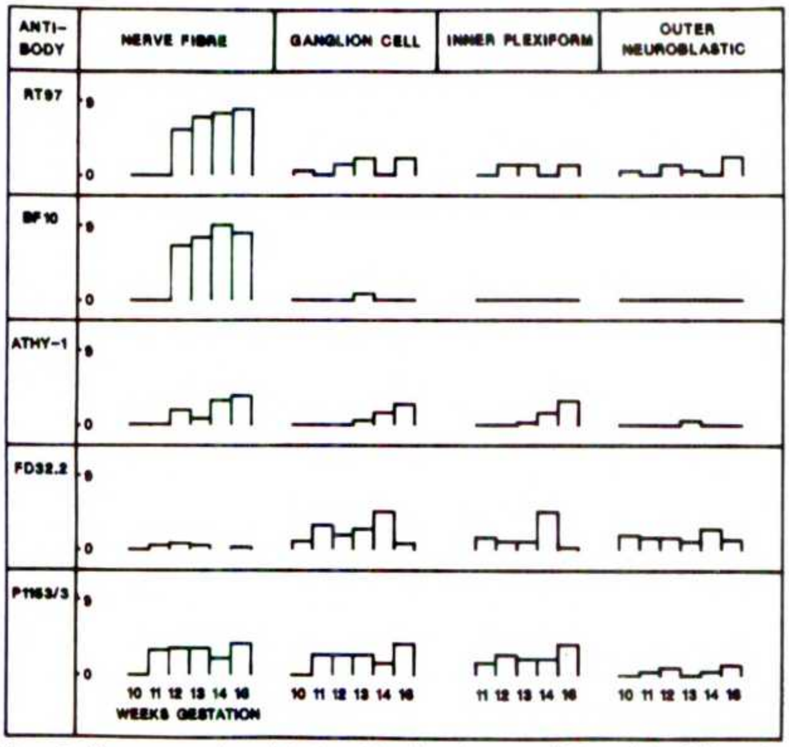

*Figure 2: Mean comparative staining intensities of reactions, scored 0 (negative) to 9 (intensely positive), for antibodies showing developmental variation in binding to fetal retinal layers of different ages. Mean values are shown.*

THY-1 antigen in the adult inner retinal layers, and to a lesser extent in the inner nuclear and outer plexiform layers. The fetal ganglion cell layers showed an ontogenic increase in antigen expression, from none at 10 and 11 weeks' gestation to mildly positive at 16 weeks. In general those layers derived from the fetal inner neuroblastic cell expressed the thy-1 antigen. Retinoblastoma showed a heterogeneous, medium to strong affinity for this antibody.

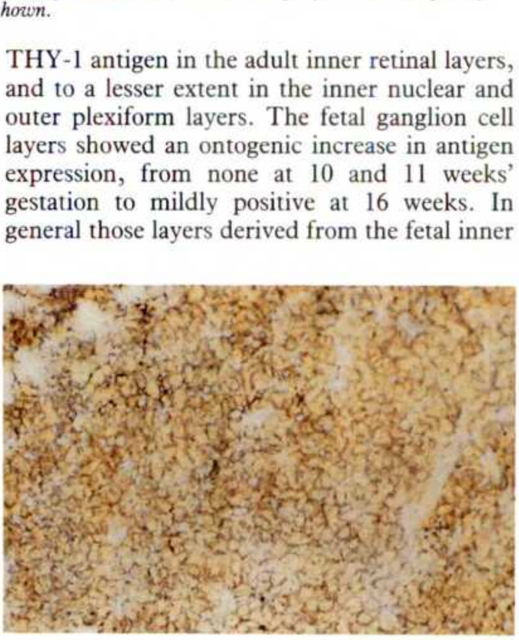

Fig 3A

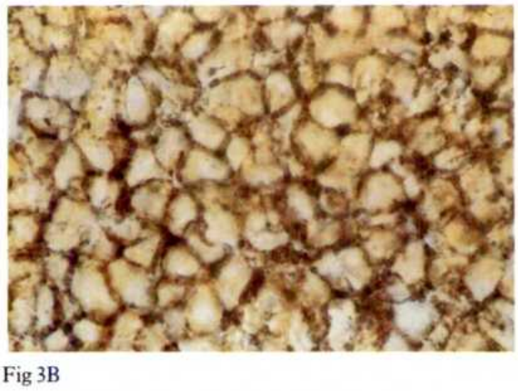

Fig 3B

*Figure 3: Retinoblastoma. (A) Sample 2, reaction with UJ127.11, neuroblastic cell surface marker, scored as 5. Original magnification ×250. (B) Sample 4 reaction with UJ13A neuroectodermal cell surface marker, scored as 7. Original magnification ×1000.*

*FD32.2 (human glioma immunogen).* Antigen in the adult retina was limited to the photoreceptor layer, and there was a weak to moderate expression throughout fetal retinas of all ages. A marked dissimilarity in the affinity of the adult and fetal choroid/sclera was noted, the adult being substantially more intense. Moderate antigen levels were located in retinoblastoma.

*FD44 (human glioma immunogen).* The cellular layers of the adult retina displayed a mild affinity for this antibody. There was mild to moderate marking of all fetal layers irrespective of age. A moderate, heterogeneous localisation was observed in retinoblastoma.

*P1153/3 (human neuroblastoma immunogen).* This antibody was found to locate cell surface antigen only in fetal tissue and retinoblastoma, with no apparent expression in adult retina, showing a degree of oncofetal specificity not found in the other antibodies assessed. Fetal retina showed low to moderate marking, particularly the inner retinal layers. Retinoblastoma displayed mild antigen expression, significantly above control levels.

*UJ13A, A2B5, H11 (neuroectodermal antigens).* These cell surface antigens were strongly expressed throughout all retinal and retinoblastoma tissue.

*FD19 (glial fibrillary acidic protein antigen).* There was mild marking of all the tissues examined, showing little specificity or differential marking of any of the cell types characterised.

*M148 (Meduloblastoma antigen).* Antigen was expressed throughout all the tissues studied, more so in fetal than in adult ocular tissue, with retinoblastoma displaying an intermediate level of expression.

*LE61 (cytokeratin), 2.3F9 (fibronectin), UJ167.11 (fetal brain), MI/N1 (neuroblastoma), UJ308 (fetal brain).* These antibodies showed no affinity for antigens present in the tissues examined. Throughout the study they acted as additional negative controls.

In summary, antibodies RT97, UJ181.4, UJ127.11, P1153/3, A Thy-1, FD32.2, FD44, UJ13A, A2B5, H11, FD19, and M148 showed affinity for retinoblastoma; of these the first seven varied in their marking of adult and fetal retinal cell types.

## COMPARATIVE IMMUNOHISTOLOGY

The antibody affinities evaluated here are those of RT97, UJ127.11, UJ181.4, BF10, ATHY-1, FD32.2, FD44, and P1153/3, and not those marking antigens which were uniformly distributed.

*Adult ganglion cell layer,* including the nerve fibre and inner plexiform layers. Tumour associated antigens marked by RT97, UJ127.11, UJ181.4, and ATHY-1 were in the retina predominantly associated with the ganglion cell layers. The BF10 neurofilament antigen was located only in the nerve fibre layer but not in retinoblastoma. FD32.2 and P1153/3 were bound by the tumour and not the ganglion cells.

*Adult inner nuclear layer.* The nuclear layer itself showed little correlation in antigen expression with retinoblastoma, and only FD44 and ATHY-1 were found to mark this cell type. When the plexiform layers were also considered there was greater antigenic homology for UJ127.11, UJ181.4, and ATHY-1.

*Adult outer nuclear layer.* Only FD44 showed any affinity for the inner nuclear cell layer, though the outer plexiform layer bound the retinoblastoma-positive antibodies UJ127.11, UJ181.4, and ATHY-1.

*Adult photoreceptor layer.* Photoreceptors showed similarity to retinoblastoma in their affinity for RT97, BF10, FD32.2, and FD44, but did not bind the tumour positive antibodies UJ127.11, UJ181.4, and ATHY-1.

*Fetal inner neuroblastic layer.* This comprises the ganglion cells and their nerve processes. The retinoblastoma-positive antibodies RT97 and ATHY-1, as well as BF10, bound to the inner retina, particularly the nerve fibre layer, after 11 weeks' gestation, and UJ127.11 and UJ181.4 were localised irrespective of developmental stage. The tumour-positive antibodies FD32.2, FD44, and P1153/3 showed greater affinity for these layers in the fetal retina than in the equivalent adult tissues.

*Fetal outer neuroblastic layer.* This primordium of the inner and outer nuclear cell layers of later retinas showed significant affinity for only FD32.2 and FD44.

None of the retinal cell types were found to have exactly parallel antigen profiles to retinoblastoma. Adult ganglion and photoreceptor cells each displayed an equivalent degree of homology with the tumour, showing similar affinities for four of the eight significant antibodies. In general those layers derived from the fetal inner neuroblastic layer bound UJ181.4, UJ127.11, and ATHY-1, and those derived from the outer neuroblastic layer were marked by FD32.2 and FD44. All of these antibodies bound to retinoblastoma, with ATHY-1, FD32.2, and FD44 being heterogeneously distributed.

## Discussion

The immunohistological profiles of six retinoblastomas have been documented and compared with those of fetal and adult retinas by means of a panel of 18 monoclonal antibodies recognising antigens associated with a wide range of tissue types.

### IMMUNOHISTOLOGY

This investigation demonstrated little difference in antigen expression between the six retinoblastomas with respect to the 18 monoclonal antibodies used in the panel, though there was marked heterogeneity within individual tumours, possibly representing foci of differentiation, indicating a mixed cell population.

*Figure 4: Sixteen-week fetal retina. (A) UJ181.4 neuroblastic marker. Nerve fibre layer scored as 9, ganglion cell layer as 3, inner plexiform layer as 3 and outer neuroblastic layer as 0. Original magnification ×100. (B) A2B5 neuroectodermal marker, scored as 9 throughout retina. Original magnification ×250. (C) P1153/3 neuroblastoma marker, scored as 2–3 throughout retina. Original magnification ×250. NF, nerve fibre layer; GC, ganglion cell layer; IP, inner plexiform layer; INB, outer neuroblastic layer; RPE, retinal pigment epithelium.*

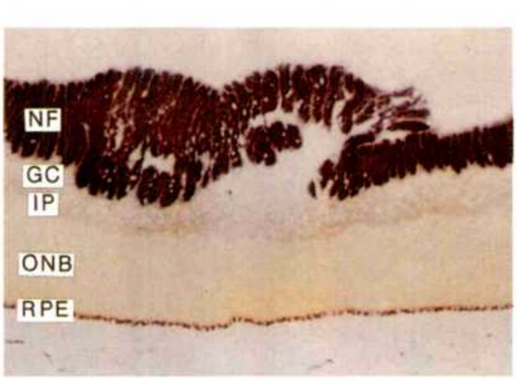

Fig 4A

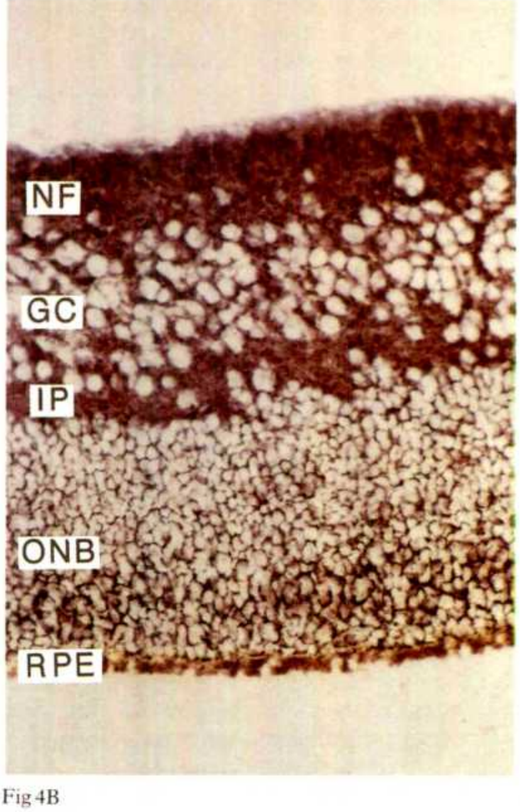

Fig 4B

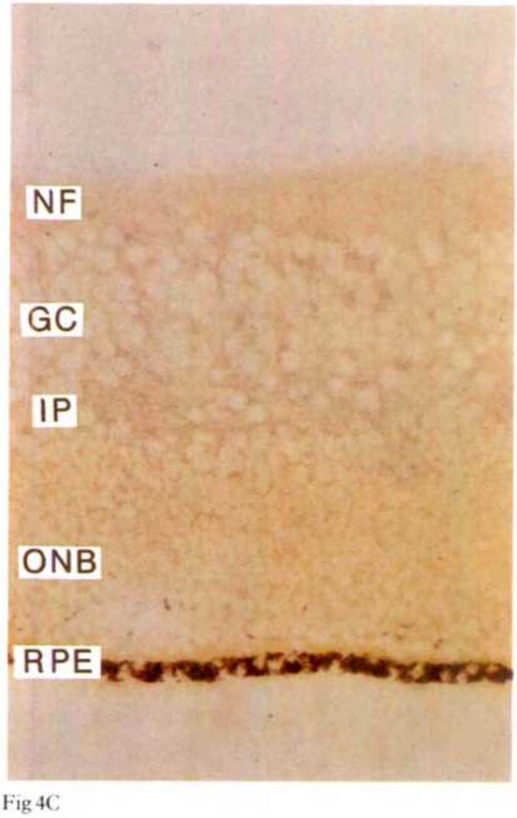

Fig 4C

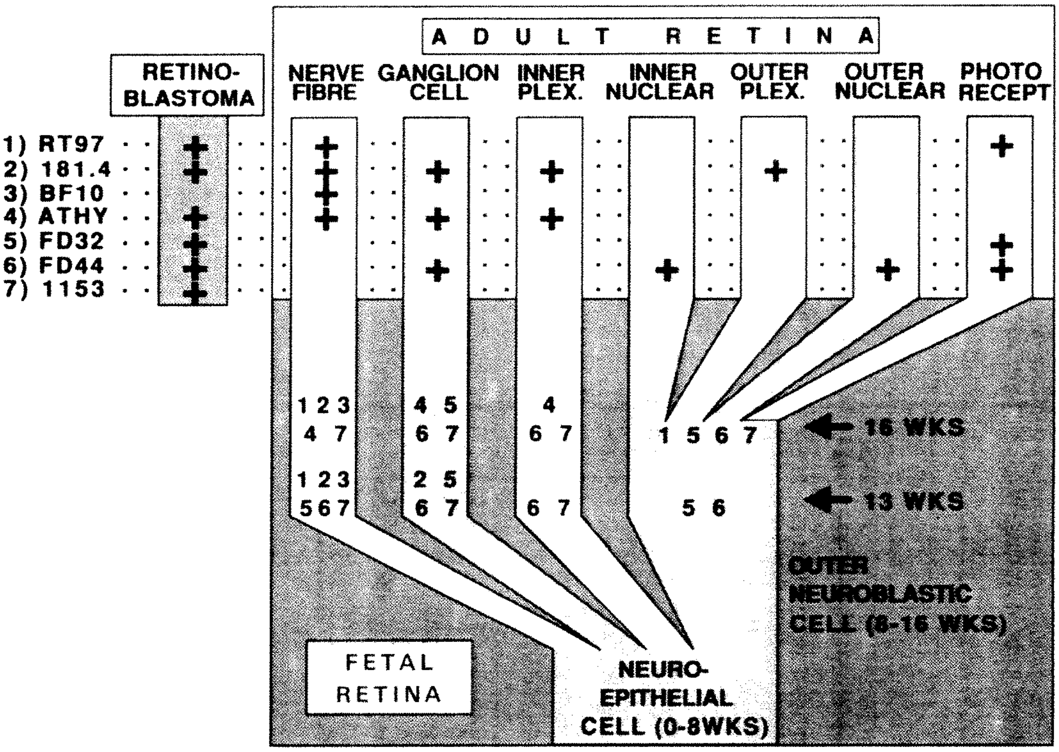

*Figure 5: Retinal cell development and antigen expression with respect to seven significant antibodies. The tissue staining scored above the overall mean staining of adult retina for the particular antibody is regarded as positive. Antibodies binding to retinoblastoma and adult retinal layers are shown as +, and those marking 13 and 16 week fetal layers are indicated by number.*

Although none of the antibodies were found to be tumour specific, some did display a degree of oncofetal specificity such as P1153/3 and, to a lesser extent, FD32.2 and FD44. All of the pan-neurorectodermal and neuroblastic markers displayed strong affinities for retinoblastoma, but UJ167.11 and UJ308, also raised against neuroectodermal tissue, were found to be negative. Moreover the neuroblastoma marker MI/N1 was found to have no reactivity for any of the tissues assessed here. Conversely FD44 does not bind to neuroblastoma *in vitro*[4] but was strongly localised to areas of retinoblastoma. UJ181.4 had previously been found to mark only neuroectodermal tumours and fetal brain,[41] yet was found here to bind equally to fetal and adult retina as well as retinoblastoma.

In this and previous investigations it has been shown that the Thy-1 antigen is associated with retinal ganglion cells[31] and neuroectodermally derived tumours,[33 34] but also with collagen fibres.[32] Similarly, FD32.2 displayed affinity for fetal retina, adult photoreceptors, and retinoblastoma, but also choroid and sclera. Thus care must be taken in interpreting the origin of retinoblastoma cells from the expression of these antigens.

The phenotypic profiles identified in this study show that retinoblastomas may be distinguished from related retinal tissue by their antigenic characteristics. Clinical immunolocalisation, however, requires that individual cells be discriminated from their environment by the consistent expression of specific cell surface markers. Operational specificity may be achieved in environments such as cerebrospinal fluid[10 12] or bone marrow samples.[1 8 13 14] For a more general application of these techniques a greater degree of specificity is required than can be afforded by any single antibody, particularly for therapeutic targeting, where the aim is selective tissue destruction. More precise localisations may be achieved by the use of a panel of monoclonal antibodies with overlapping affinities for multiple staining techniques or combined immunotherapy.

Owing to the heterogeneity of retinoblastoma with respect to some antigens, a panel of monoclonal antibodies best able to characterise a tumour mass, which expresses all potential antigens, may differ from one used to localise individual tumour cells.

## HISTOGENESIS

The panel of antibodies was used to compare the antigen profile of retinoblastoma with those of adult and fetal retinal cells in order to help define the origin of the tumour.

The stem cells of tumours derived from adult tissue have been defined on the basis of residual differentiation characteristics. It is thought that retinoblastoma, arising from immature tissue, as well as retaining existing characteristics may express those within the potential of its stem cell as tumour differentiation occurs[15 18 20 23 42] and hence recapitulate some normal retinal development.

A comparison of the immunohistological characteristics of retinoblastoma and adult retina indicated homology with both ganglion and photoreceptor cells, suggesting that the tumour cells can exhibit characteristics of both these cell types simultaneously or can undergo alternative differentiation under the influence of environmental factors. The antigenic heterogeneity seen in retinoblastoma supports the latter case. The greater oncofetal localisation of P1153/3, FD32.2, and FD44 resulted in a closer homology between retinoblastoma and fetal cells than for adult cells. The homology identified between early fetal ganglion cells and retinoblastoma could not be compared with that of photoreceptor cells, as these cell types are absent at this
]

stage of development. Despite the parallels in antigen profiles, characteristic differences between retinoblastoma and differentiated retinal layers identified in this and other studies[15 17 18 23 24] preclude the tumour arising from any particular retinal cell type.

Figure 5 illustrates the retinal cell development[43] and antigen expression of retinal cells. The closest single comparative cell type with retinoblastoma was found to be the 13–16-week inner retinal cell, though it was found that the tumour expressed antigens associated with both inner and outer retinal layers. Moreover other studies have shown that retinoblastoma exhibits characteristics of photoreceptor differentiation, such as retinal s-antigen,[15 23 24] opsin,[15] inter-retinoid binding protein,[15 44] neuron-specific enolase,[15 17 25] and cyclic guanosine monophosphate.[15] Hence a putative retinoblastoma progenitor cell has potential for photoreceptor as well as inner retinal cell differentiation. In relation to the retinal cell development this implies a tumour origin from a primitive neuroepithelial cell type predominating prior to the 8th week of gestation; more developed cells would not combine the capacity to express both photoreceptor and ganglion cell characteristics.[43] Such a primitive pluripotential stem cell would be expected to differentiate according to its environment, producing a mixed cell population with the phenotypic heterogeneity found in retinoblastoma, and no exact parallel in antigen expression would be expected with any single mature retinal cell type. The number of such vulnerable neuroepithelial cells is greatest before eight weeks' gestation and would steadily decline throughout later development, resulting in a decreasing incidence of retinoblastoma with increasing age.

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# Contact lenses for infant aphakia

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## Abstract

**We prospectively studied for three years the optical correction by contact lenses of 83 aphakic infants (141 eyes) who generally also had systemic and other ocular anomalies: 85% of the patients tolerated the lens wear for the whole study period. Complications occurred in 46 eyes and led to cessation of lens wear in two cases. Ten patients abandoned the lenses for other reasons. Thirty-four eyes needed subsequent intraocular surgery, mostly minor, and nine patients had strabismus surgery. Contact lenses are a versatile, safe, successful, and cost effective treatment for aphakia in infancy against which, before their widespread introduction for primary optical correction of infant aphakia, other methods of aphakic treatment need to be compared.**

In 1959 Sato and Saito[1] presented two children fitted with hard contact lenses, and other early reports using hard lenses[2-4] described difficulties but good visual results. Soft contact lenses were used initially for adult aphakia,[5] but complications occurred, such as the 'tight-fit syndrome', corneal vascularisation, lens deposits, bacterial conjunctivitis, hypersensitivity, and corneal oedema, all partly due to fitting techniques or to the thickness of lenses. Preservatives were introduced to reduce the incidence of conjunctivitis, but hypersensitivity occurred to these agents.[6 7] Hard contact lenses for the correction of infantile aphakia have also been advocated,[8] including the use of silicone rubber lenses.[9]

Although spectacles are inexpensive, easily changed, and generally safe, they may be inappropriate for infants, as they are heavy, ugly and they create a prismatic effect, visual field constriction, and in monocular aphakes they are usually impracticable.[10]

Intraocular lenses have been used since the early 1970s,[11] but the difficulty in obtaining adequate parameters for infants, the subsequent growth of the eye after implantation, and the number of complications[12] make them unacceptable in view of the life-long nature of the treatment and the uncertainty of the lenses' long-term performance. There is little evidence to support the safety of even the newest generation of intraocular lenses in infants in the long term, and the rapid growth of the eye during the first year of life makes a permanent unchangeable power inappropriate.[13]

Epikeratophakia is a promising solution,[14 15] though the undercorrection of the refraction in infants and other problems, including the rapid change in refractive power of the eye in the first year of life,[16] suggest that it should be reserved as an alternative in some older patients who are intolerant to contact lenses.

Infantile aphakia needs an adaptable method of optical correction that allows the parameters to be easily changed, that has a low complication rate, and a high quality of optical correction. The method must also be practical and inexpensive to families and to the providers of medical care.

We present a review of our experience with the use of soft contact lenses, the incidence of complications, tolerance, co-operation from patients and parents, and the costs engendered.

## Subjects and methods

From 31 December 1984 we have provided a contact lens service for aphakic infants. Included in our prospective study are all infants made aphakic within the first year of life, until 1 January 1988. Cases where anatomical or functional defects precluded useful vision were not optically corrected postoperatively.

The patients with bilateral cataracts usually had the operations done within three days of each other, with the first eye being patched in between to prevent the second eye from developing amblyopia. Two uniocular cases were traumatic, and one patient with Marfan's syndrome had a dislocated lens; the rest were congenital cataracts. The majority of patients came from outside London; nine patients lived abroad (Table I).

The lenses were fitted during the week following surgery; in bilateral cases both lenses were fitted at the same time. They were re-examined the next week, one month later, and then every three months, unless more frequent visits were required because of complications or lens handling difficulties. Parents were instructed to insert, remove, and clean the lenses daily from the beginning, with special emphasis on vigilance for complications and side effects. Lenses of high water content were used at first, and when the child no longer slept during the day they were changed to lenses of a lower water content.

Initially the lenses were cleaned daily with a surfactant cleaner and then sterilised by boiling in preservative-free saline. Once the parents were more used to the lenses a chlorine-based cleaning regimen (Softab) preceded by surfactant cleaning was used. Protein removal

TABLE I *Patient's travelling distance in miles from central London*

| *Number of miles* | *Number of patients* |
|---|---|
| Peripheral London (0–15) | 16 |
| 16–30 | 15 |
| 31–50 | 10 |
| 51–80 | 6 |
| 81–120 | 7 |
| 121–160 | 3 |
| 161–200 | 7 |
| More than 200 | 5 |
| From abroad | 9 |
| No information | 5 |
| Total | 83 |

Note: 1 mile=1·6 km.

tablets were rarely used, as the lenses tended to become lost or broken before this became necessary.

After retinoscopy an overcorrection of around 2–3 dioptres was prescribed. The back optic radius (BOR) was selected on a trial basis according to the age of the patient on the known average corneal radius, which in neonates was 7·1 mm, and changes were made as needed. The diameter of the lenses and their fit was determined empirically from the corneal diameter and careful observation on the stability of the lens on the eye, with the size varying between microphthalmic and normal corneas. At each visit an ophthalmic examination was performed, including funduscopy and retinoscopy and, when possible, slit-lamp examination. The child was examined by an orthoptist when signs of a squint were apparent. Spectacles were prescribed as an alternative to contact lenses in case the contact lenses caused problems, and parents were given spare lenses, and extra lenses were mailed when necessary. A detailed verbal description of the risks and difficulties was given to the parents at the outset; more recently they have been given a booklet detailing the treatment.

## Results

The surgical technique in 121 eyes was lensectomy with anterior vitrectomy. A lens aspiration without vitrectomy was performed in 19 cases. One eye had an intraocular lens implant, in a patient who lived far from London, and had a life span likely to be limited to three years.

The known age of onset of the visual deprivation from the cataracts was at birth in 109 of the eyes (77·3%). In six eyes the age of onset was unknown (Table II). 12·2% of the bilateral cases were operated on by 2 months and by 4 months of age, and 53·8% of the unilateral cases had surgery by 2 months and 85% by 4 months.

Twenty-six had associated systemic abnormalities (Table III), and 39 patients had other eye anomalies apart from the cataracts (Table IV). As regards postoperative complications, 11 eyes required pupilloplasties (Table V), mainly to maintain a clear visual axis when this became inadequate. Six eyes developed glaucoma, of which two improved on medical therapy. Four eyes required anterior vitrectomy, three of them to reduce increased intraocular pressure secondary to pupil block. Two of these improved with surgery; the other developed uncontrolled glaucoma with a blind, buphthalmic eye. One eye developed glaucoma of unknown cause, controlled with a trabeculectomy. The eyes with non-pupil-block glaucoma had anomalies additional to the cataracts.

Removal of residual lens matter with posterior capsulotomy was required in both eyes of one patient. Of the 19 patients who had lens aspiration without vitrectomy 14 required posterior capsulotomy. Nine patients underwent squint surgery. Five patients needed removal of sutures under general anaesthetic, and nine patients had examinations under general anaesthetic for various reasons. 141 eyes of 83 patients were fitted with soft contact lenses. Of these patients 67 were under 1 year of age, 58 were binocular aphakes, and 25 were uniocular.

Forty-three eyes had complications due to the use of contact lenses (Table VI). Twelve developed red eye, with no evidence of bacterial or viral infection; loose sutures were responsible for this in five cases. In those cases not due to loose sutures the eyes settled within a few days once the lenses were removed. In bilateral cases if one lens was removed the other was also, to equate the optical state of the two eyes. Eighteen patients had bacterial conjunctivitis which always improved with antibiotic treatment. Three patients had recurrent infections, probably due to improper cleaning of the lenses. Three patients who had hypoxic ulceration due to improper handling and inadequate removal of the lenses improved after regular and daily removal of lenses, but two of these were changed to spectacle wear.

Three patients developed intolerance, with red eye, discomfort, and watery discharge when the lenses were in, but they were completely asymptomatic when the lenses were out. None of these were related to giant papillary conjunctivitis, but when changed to HEMA (38% water content) soft contact lenses or silicone rubber

TABLE II *Age of onset of visual deprivation from cataract*

| *Onset (months)* | *Bilateral* | *Unilateral* |
|---|---|---|
| 0 | 48 | 13 |
| 1·5 | 1 | 1 |
| 2 | 2 | – |
| 3 | 1 | – |
| 5 | – | 2 |
| 6 | 1 | 2 |
| 8 | 2 | 1 |
| 9 or more | – | 6 |
| Unknown | 3 | – |

TABLE III *Systemic abnormalities (83 patients)*

| | | |
|---|---|---|
| | Without other abnormalities | 57 |
| | With other abnormalities | 26 |
| a. | Down's syndrome | 7 |
| b. | Congenital rubella | 7 |
| c. | Marfan's syndrome | 1 |
| d. | Cerebro-oculo-facial-skeletal syndrome (Pena Shokeir) | 2 |
| e. | Cardiomyopathy; lactic acidosis | 1 |
| f. | Severe neonatal asphyxia | 1 |
| g. | Cerebral palsy | 1 |
| h. | Persistent fetal circulation; sepsis | 1 |
| i. | Ectopic anus | 2 |
| j. | Hearing problems | 2 |

TABLE IV *Other ocular abnormalities (83 eyes)*

| | |
|---|---|
| Persistent hyperplastic primary vitreous | 4 eyes |
| Posterior lenticonus | 4 eyes |
| Microphthalmos | 2 eyes |
| Ant segment dysgenesis | 21 eyes |
| Ectropion uveae | 2 eyes |
| Dislocated lenses | 2 eyes |
| Rubella retinopathy | 1 patient |
| Heterochromia | 1 patient |
| Blepharospasm | 1 patient |
| Iridopupillary membrane | 1 patient |

TABLE V *Postoperative surgical complications ($n = 141$ eyes)*

| | |
|---|---|
| Pupilloplasty | 11 |
| Anterior vitrectomy | 4 |
| Glaucoma | 6 |
| (*a*) Improved medically | 2 |
| (*b*) Anterior vitrectomy | 3 |
| (*c*) Trabeculectomy | 1 |
| Residual lens matter extraction | 2 |
| Posterior capsulotomies | 14 |
| Squint surgery | 9 |
| Removal of sutures under GA | 5 |
| Examination under anaesthetic for other reasons | 9 |
| Total | 60 |

TABLE VI *Number of eyes with contact lens induced complications (n=141)*

| | |
|---|---|
| Red eye | 12 |
| Infection | 18 |
| Hypoxic ulceration | 3 |
| Fine vascularisation | 3 |
| Intolerance | 3 |
| Oedema | 2 |
| Punctate keratitis | 2 |
| Total | 43 |

TABLE VII *Number of patients in whom contact lenses were discontinued (n=83)*

| | |
|---|---|
| Hypoxic ulceration | 2 |
| High turnover | 3 |
| Parent's difficulties in handling contact lens | 4 |
| Others (preferred glasses) | 3 |
| Total | 12 |

lenses they were symptom-free. Two patients had corneal oedema which subsided after removal of the contact lenses and change of parameters. 1 mm or more of corneal pannus developed in three patients. Two of them were changed to Polycon gas-permeable hard lenses, with reduction in the pannus; the other was changed to spectacle wear. Punctate keratitis necessitating temporary lens removal was diagnosed in two patients, and three patients had such a high incidence of loss or renewal of lenses (turnover) that their use was abandoned.

Twelve (14·5%) of the patients abandoned the lens wear (Table VII), two with hypoxic ulceration, three with a high lens turnover, and four with visually handicapped parents; three older children had no major problems but preferred to use spectacles. Five other patients stopped the use of contact lenses for more than one month but started them again.

81·1% of the eyes in the bilateral aphakes and 66·8% of the unilaterals had less than one lens replaced per month (Figs 1, 2). In the first six months of treatment there was a higher incidence than in later months of lens replacement either for changes in parameters or because the lenses were lost, broken, or rubbed out (Fig 3). 76·6% of the bilateral cases and 80·76% of the unilateral required less than one change of lens for reasons of change in parameters. Seven eyes were excluded from this figure because they had been treated for less than three months.

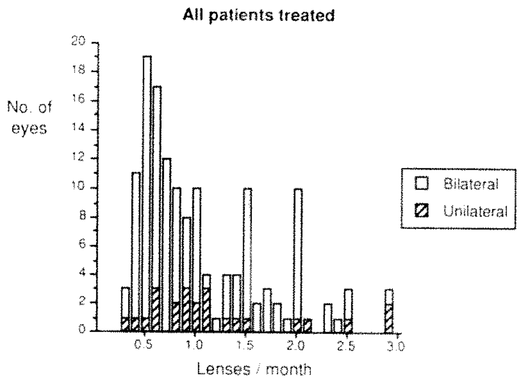

*Figure 1: Total number of lenses per month per eye.*

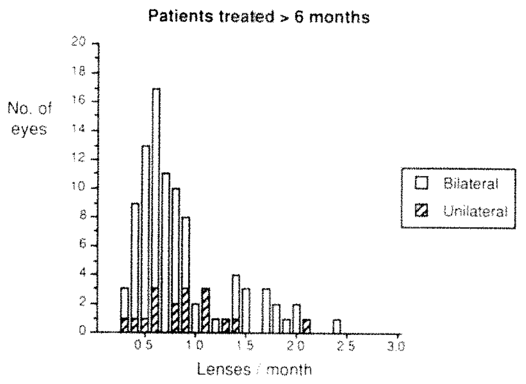

*Figure 2: Number of lenses per month per eye in patients treated for more than six months.*

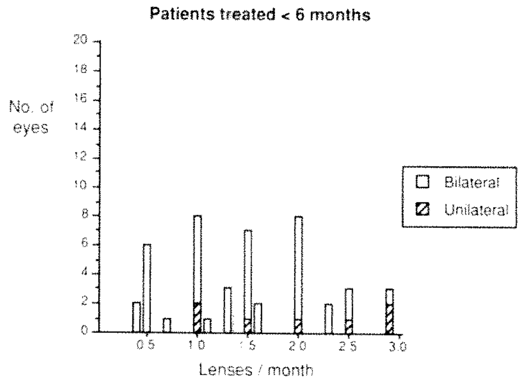

*Figure 3: Number of lenses per month per eye in patients treated for less than six months. There is a higher turnover in the first six months.*

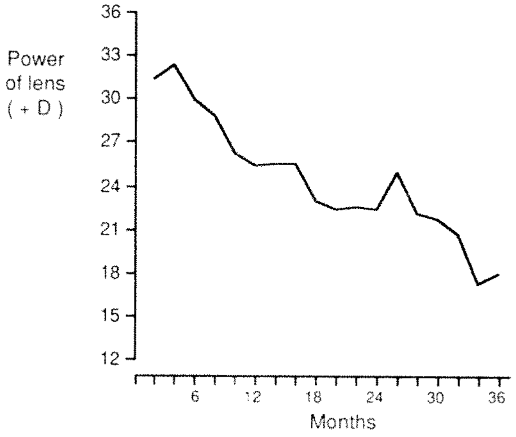

*Figure 4: Power of the contact lenses compared with the age of the patients. As the age increases there is a steady decrease in the power of the contact lenses.*

Figure 4 shows the average power of the lenses up to 3 years of age (the dioptric value range from 12 to 34 dioptres), clearly demonstrating how the required power of the lenses decreased as the infants grew. Microphthalmic eyes remained small, requiring high power lenses, even with age.

The number of lenses issued during this period was 1483. At a cost of £18 per lens, this totalled £26 694. The total cost of solutions was £3978. On average, the cost of lenses per month per patient was £28.50. In addition to this the costs of running the clinic must be taken into account, including the services of an optometrist, an ophthalmologist, an orthoptist, and nurses.

## Discussion

Microsurgical techniques have considerably improved the outcome of infantile cataract surgery, and our results show that the number of reoperations is small, the majority of them being pupilloplasties, often to recentre the pupil when it has been decentred, usually by vitreous strands. Nine patients at risk for glaucoma required repeated examinations under anaesthetic, but the incidence of glaucoma was low, unless the eye was otherwise anomalous or microphthalmic.[13] We do not routinely remove the corneal sutures, but when these are loose, especially when contact lenses are used, they can cause irritation until removed.

With our contact-lens fitting protocol there is a low incidence of side effects attributable to the use of the lenses. We have seen no cases of giant papillary conjunctivitis.[17-19] The low incidence of bacterial conjunctivitis, hypoxic ulceration, and corneal oedema is probably due to the daily lens removal and sterilisation regimen.

Although it may be thought that daily handling of the lenses increases the risks of infection, our experience suggests the opposite, and this may be due to the careful handling by well trained and dedicated parents. Electron microscopy[20] has shown that bacteria attach to the surface of soft contact lenses and 'proliferate' unless the lenses are removed, cleaned, and sterilised frequently.[21] Solutions with preservatives such as thiomersal or chlorhexidine may cause allergic reactions, but our handling scheme avoids this problem. The lens deposits associated with this method were usually avoided because of the high lens turnover.

The daily removal of lenses may appear daunting for parents, but most of them were willing and co-operative and learned within the first weeks. Four families could not get used to handling the lenses: in two cases, the mothers were blind, and in another the patient had very microphthalmic, sunken eyes.

The parents were impressed with the need to remove the lenses if there were any signs of infection, red eye, or discomfort. General practitioners cannot be expected to be experienced with the use of lenses and cannot usually advise on handling them or on the treatment of complications, so removal by the parents, especially if they live far from ophthalmological care, is especially important as a first step. When the child was older, or where corneal damage was evident, they were changed to more durable low-water-content lenses.

Three patients, two of whom had worn soft lenses for three years, developed superficial corneal vessels of less than 1 mm. The low incidence in this study was presumably due to the short period of follow up and the daily wear regimen.

Only 12 (14·5%) of the 83 patients discontinued use of their contact lenses. Three of these did not have a clinical reason to do so. They found it more convenient to use the spectacles, or they had an excessively high turnover rate. This rate is remarkably similar to the recently reported failure rate of Levin *et al*,[21] and there are sufficient other reports of successful contact lens wear in aphakic infants[22-25] to suggest that it is a technique that can be adopted by many departments already experienced with adult contact lenses provided some differences in management are used. Most parents were reluctant to change their child to spectacle wear even if the wearing of lenses had been difficult.

The loss of contact lenses in adults is relatively low.[26] Lens loss in infants is necessarily higher owing to the frequent change in parameters, the high rate of loss and breakage of lenses, and the ocular complications. Because of the necessary changes in contact lens parameters it is not practical to fit many children in the United Kingdom with silicone rubber lenses, which are slow and expensive to obtain and which have inherent surface problems. This material was therefore only occasionally used. Figures 4 and 5 show the change in power during the first year of life, and the frequent need to change parameter. This is in contrast to the study by Pratt-Johnson and Tillson,[8] who did not change hard lens parameters during the first five years of life. 81·1% of the eyes required fewer than one lens per month; many of these lenses can be reused once sterilised. The optical correction of infantile aphakia during the first three years of life costs £440 in contact lenses and £112 in solutions (aerosol saline and cleaning solution), making a total of £562. These costs do not include the services of an ophthalmologist and an optometrist, nor the considerable travel costs for parents (Table I).

The optical correction of infantile aphakia with daily wear soft contact lenses is an effective and economical method. It has the adaptability to respond to changes in the parameters, and the parents can easily insert and remove the lenses. It gives a high quality optical correction with a low incidence of complications. It is cost effective, though there are many hidden costs for the parents. With a contact lens tolerance rate of 85·5% it is difficult to see a need for alternative, relatively untried optical correction, such as intraocular lenses, for the primary correction of infantile aphakia.

This project has been supported by the Iris Fund for the Prevention of Blindness, and the Help a Child to See Fund.

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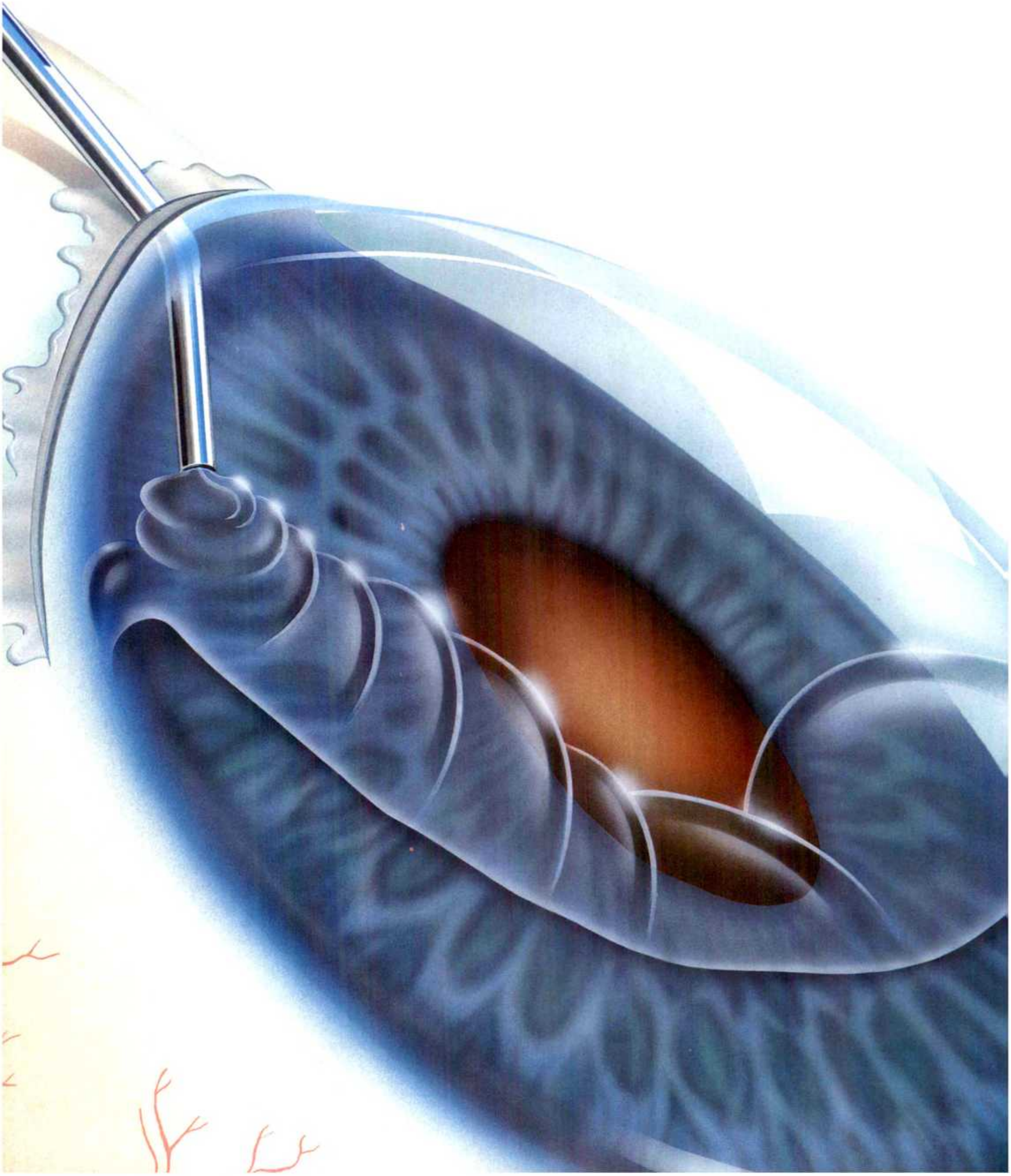

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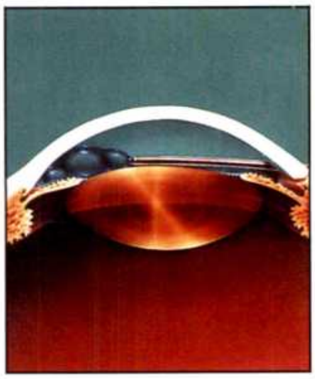

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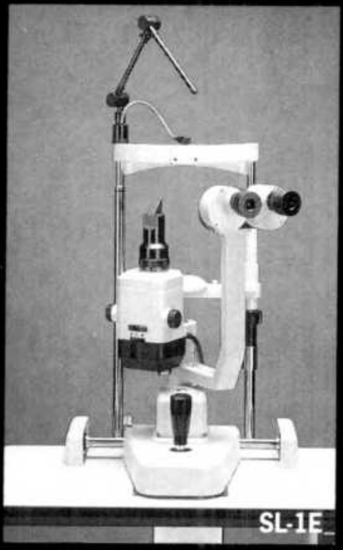

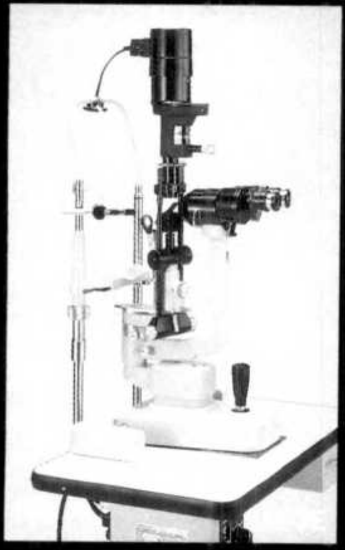

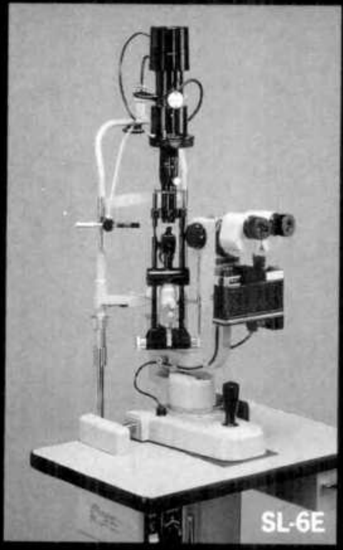

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# Binocularity following surgery for secondary esotropia in childhood

Catherine N Smoot, John W Simon, Leonard B Nelson

**Abstract**

**Binocularity was assessed in children who developed large, constant esotropia following bilateral lateral rectus recessions for intermittent exotropia. Nine such patients were identified who warranted medial rectus recession. Seven were finally aligned within 6 prism dioptres after secondary surgery. Stereopsis measured 50 seconds or better in six of these patients and 200 seconds of arc in the seventh. Two patients had residual deviations: one child with 30 prism dioptres of residual esotropia had 400 arc seconds and the remaining patient, with 12 prism dioptres of exotropia and marked anisometropia, did not show stereopsis. Children with constant acquired esotropia for as long as two years may still have normal stereopsis after surgical alignment. The risk of losing binocularity because of a large overcorrection following exotropia surgery may be smaller than previously assumed.**

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Most authors agree that children with strabismus, especially if it is constant, are at risk of losing binocularity.[1-4] Many believe that, because intermittent exotropia often increases in frequency during childhood, affected patients should be operated on early to counter this threat to binocular function.[2,5-7] Similarly, most authors consider treatment of children with acquired esotropia to be urgently indicated.[3] Esotropia acquired from surgical overcorrection of exotropia is often termed secondary or consecutive esotropia.

It is uncertain how long a constant deviation can be tolerated in childhood without loss of binocular potential. We observed that some patients following secondary surgery have normal binocularity despite prolonged periods of constant consecutive esotropia. In order to determine what binocularity can be expected in patients with this history, we reviewed our patients who required esotropia surgery following repair of childhood exotropia.

TABLE I *Motor and surgical data*

| Case | Age BLR recess (mo) | Preop. X(T)* | Amt BLR recess (mm) | Age MR recess (mo) | Preop. ET | Amt MR recess (mm)† | Postop. F/U (mo) | Final align |
|---|---|---|---|---|---|---|---|---|
| 1 | 57 | 25 | 5·0 | 61 | 30 | 4·5 | 94 | LX(T) 6 |
| 2 | 28 | 30 | 6·5 | 38 | 20 | 3·0 | 62 | Ortho |
| 3 | 38 | 35 | 7·0 | 70 | 40 | 5·0 | 14 | Ortho |
| 4 | 22 | 60 | 10·0 | 42 | 70 | 6·5 | 25 | RXT 12 |
| 5 | 32 | 40 | 7·5 | 60 | 50 | 5·5 | 39 | LET 30 |
| 6 | 42 | 30 | 6·0 | 78 | 25 | 6·0 | 12 | Ortho |
| 7 | 84 | 25 | 6·0 | 90 | 25 | 4·0 | 12 | Ortho |
| 8 | 54 | 30 | 7·0 | 66 | 30 | 4·5 | 24 | X 6 |
| 9 | 30 | 35 | 7·0 | 72 | 20 | 5·5 | 6 | Ortho |

BLR recess=bilateral lateral rectus recession. Preop X(T)=preoperative intermittent exotropia. Amt=amount. MR recess=medial rectus recession. Postop. F/U=postoperative follow-up. Align=alignment. XT=exotropia. ET=esotropia. X=exophoria. *Alignment given in prism dioptres of distance deviation with correction; †All medial rectus recessions were bilateral except cases 6 and 9, which were unilateral.

## Patients and methods

The records of all patients aged 6 months to 7 years who underwent recessions of both lateral recti (by JWS or LBN) for exotropia were reviewed. Nine were identified who developed constant secondary esotropia large enough to warrant medial rectus recessions. Patients with small postoperative deviations were not a subject of this study. All patients had 20 or more prism dioptres of esotropia.

The age and ophthalmic alignment of all nine patients prior to both operations were noted. Also tabulated were the amount of lateral rectus and medial rectus recessions, the final alignment, and the duration of follow-up.

Sensory data included: visual acuity with most recent refraction, Worth-4 dot test results at ⅓ m and 6 m, and stereoacuity by Titmus or Randot testing. Stereopsis was assessed in standard room illumination at a distance of 14 inches (36 cm). Stereoacuity was defined by the level of the first error which could be confirmed on retesting. Any adjunctive treatment, such as occlusion therapy for amblyopia, optical or prismatic correction, and orthoptic exercises, was also noted.

## Results

As shown in Table I, the nine identified patients underwent lateral rectus recession at 22 to 84 months of age (mean 43, SD 19 months). Preoperatively, exotropia was intermittent in all cases, ranging at distance from 25 to 60 prism dioptres (mean 34, SD 11 prism dioptres). Generally, the deviations were initially better controlled at near. In all cases the parents stated that progression of frequency or duration occurred gradually. In this retrospective study, assessment of binocularity was available prior to exotropia surgery in only the first patient. This child preoperatively had Worth-4 fusion at distance and near with 100 arc seconds stereopsis.

Postoperatively, esotropia ranged from 20 to 70 prism dioptres (mean 34, SD 16 prism dioptres) and was constant in all of the patients. Hyperopic correction was prescribed where appropriate (Table II) but was inadequate to control the esotropia in any case. Prisms were likewise ineffective in patient 1. In general, most notably in patients 3 and 4, gradual increase in the esodeviation was observed prior to secondary surgery. Medial rectus recessions were performed when, after discussion of surgical risks and benefits, parents elected to proceed. The patients ranged in age at second surgery from 38

TABLE II *Sensory and refractive data*

| *Case* | *Refraction* | *Acuity* | *Amblyopia* | *Patch* | *Glasses* | *Stereo** | *W4†* |
|---|---|---|---|---|---|---|---|
| 1 | OD −0·25 | 20/20 | No | No | Yes | 30 | Fuse |
| | OS −0·50+0·50×85 | 20/20 | | | | | |
| 2 | OD −3·00 | 20/20 | No | No | Yes | 25 | Fuse |
| | OS −3·00 | 20/20 | | | | | |
| 3 | OD +1·00+0·75×65 | 20/20 | No | No | Yes | 50 | Fuse |
| | OS +1·75+0·50×90 | 20/20 | | | | | |
| 4 | OD −6·75+1·50×90 | 20/30 | OD | Yes | Yes | None | Diplopia |
| | OS −0·25+1·75×60 | 20/20 | | | | | |
| 5 | OD +0·75+0·50×5 | 20/20 | OS | Yes | No | 400 | Suppress OS |
| | OS +1·00 | 20/25 | | | | | |
| 6 | OD +2·00 | 20/20 | No | No | No | 50 | Fuse |
| | OS +2·00 | 20/20 | | | | | |
| 7 | OD +0·50 | 20/20 | No | No | No | 40 | Fuse |
| | OS +0·50 | 20/20 | | | | | |
| 8 | OD +1·00+0·25×90 | 20/25 | No | No | No | 200 | Fuse near, suppress far |
| | OS +1·00+0·25×90 | 20/25 | | | | | |
| 9 | OD +1·50 | 20/25 | No | No | No | 50 | Fuse |
| | OS +1·50 | 20/25 | | | | | |

*Sreteoacuity measured in arc seconds by Randot test in cases 1 to 5 and Titmus in cases 6 to 9.
†Worth-4 dot test at near and distance.

to 90 months (mean 64, SD 16 months). The interval between surgeries ranged from 4 to 42 months (mean 21, SD 14 months).

Follow-up after secondary surgery ranged from 6 to 94 months (mean 32, SD 29 months). No patient has undergone a third surgical procedure. When the patients were last examined, alignment in seven of the nine was within 6 prism dioptres of orthophoria at distance and near. Table II shows that, of the seven aligned patients, six showed stereoacuity of 50 arc seconds or better. The one remaining aligned patient had 200 arc seconds of stereopsis. All seven aligned patients fused the Worth-4 lights at ⅓ m and six of the seven fused at 6 m.

One of the nine patients had 30 prism dioptres of persistent esotropia following medial rectus recession but still had gross stereopsis of 400 arc seconds. Worth-4 testing revealed suppression of the left eye at distance and near. The remaining patient, with 12 prism dioptres of recurrent exotropia and anisometropia, failed to show stereopsis or Worth-4 fusion at any test distance. The three patients with stereopsis of 200 seconds or poorer were initially operated upon at a mean age of 36 months. The remaining children, with 50 seconds or better, had a mean age of 46·5 months at first surgery.

## Discussion

The timing of surgery for intermittent childhood exotropia has been the subject of considerable controversy. Although Pritchard and Flynn[8] have presented evidence of abnormal binocular interactions even during periods of alignment, most authors have observed normal stereopsis and Worth-4 test results when the deviation is controlled.[3] Proponents of early surgery argue that in children with intermittent exotropia the deviations tend to worsen with time.[2,5-7] They fear that increasing frequency of exotropia during the period of visual system plasticity will then generate predictable abnormal sensory adaptations. According to this argument deepening suppression and anomalous retinal correspondence will probably preclude useful binocularity if surgery is deferred.

Von Noorden, Jampolsky, and others with the opposing viewpoint have questioned the frequency of motor deterioration but not the potential threat to binocularity.[1,3,9] It is because young children may be at risk of postoperative small angle esotropia, with its comparable risk to normal binocular function, that some believe surgery should be delayed. They argue that early surgery may exchange a preoperative state of intermittent fusion for a surgical overcorrection, with constant monofixation and possible amblyopia. This sequence has been most commonly observed in children operated on before the age of 4 years.[6] In our series, by excluding patients with small postoperative deviations, we have attempted to eliminate patients with intermediate binocular status after primary surgery.

The patients we report on all developed large constant esotropias following repair of intermittent exotropia. Because the secondary deviations were observed for prolonged periods during childhood, we expected all to have poor binocular function. Yet all seven of the successfully aligned patients had stereopsis. Six had stereoacuity of 50 arc seconds or better and Worth-4 fusion at distance and near. There did not seem to be any correlation between the duration of the constant esotropia and the final stereopsis that was observed.

The one patient who did not show stereopsis had marked anisometropia. In view of previous observations that binocular potential is often poor in patients with anisometropia[10] this child's absence of stereopsis is not surprising.

We recognise that Randot testing of stereopsis is preferable to Titmus in that it avoids monocular cues. As this is a retrospective study, stereopsis has been measured only by the latter test in four of our patients. Because the Titmus test results were better than might be expected from such artefacts of testing and because they were confirmed on repeated visits and corroborated by Worth-4 testing, we believe the results are accurate in these four patients.

To our knowledge this is the first series of patients with normal binocular function following a defined period of constant strabismus in childhood. Clinical reports rarely specify the onset and duration of abnormal visual experience. The unexpected binocularity in our patients presumably reflects the establishment of cortical visual connections during early childhood, prior to the onset of intermittent exotropia or during its latent periods. Our results show that constant strabismus acquired in childhood does not cause loss of binocular potential in all cases.

Our experience will not resolve the controversy on timing of surgery for intermittent exotropia. Early surgery may not jeopardise binocular potential as previously feared, even in children with large overcorrections. On the other hand delaying surgery may not be harmful if binocularity is firmly established. It is conceivable that small-angle overcorrection of younger children may be more dangerous to binocular development than large consecutive esotropia. We acknowledge that our patients with better binocularity were operated on at a later mean age than those with poorer binocularity. At present we favour a conservative approach, operating when each patient's symptoms, whether cosmetic or functional, are substantial.

This study was supported in part by National Institutes of Health training grant EY0703702, by an unrestricted grant from Research to Prevent Blindness, Inc (Drs Smoot and Simon), and by a grant from Fight For Sight Inc, NY, NY to the Fight for Sight Child Eye Center, Wills Eye Hospital (Dr Nelson).

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# Results of a randomised trial of treating abnormal hypermetropia from the age of 6 months

R M Ingram, P E Arnold, S Dally, J Lucas

**Abstract**

**Children who were abnormally hypermetropic at the age of 6 months were randomly allocated treatment with spectacles or no treatment. The eventual incidence of squint was the same in both groups (approximately 24%). The last known visual acuity of the two groups was not significantly different either. Therefore there is no indication to screen infants with a view to preventing squint/amblyopia by optical correction of hypermetropia. If, however, the children allocated treatment are divided into two subgroups – those who wore glasses consistently and those who probably or certainly did not do so – the incidence of squint was the same, but the last known acuities of those who consistently wore glasses may be better than those who did not do so. This suggests that it may yet prove possible to prevent severe amblyopia.**

A previous paper[1] described an attempt to prevent squint and/or amblyopia by spectacle correction of abnormal hypermetropia from the age of 1 year. In the event the attempt proved unsuccessful. A possible explanation for this lack of success could be that treatment was started too late. This is a report of a similar randomised trial of treatment started at the age of 6 months.

## Patients and methods

### PATIENTS

Children living within the boundaries of the Kettering and District Health Authority and those living in Market Harborough were refracted at the age of 6 months. Those who had +4·00 or more D hypermetropia in any one or more meridia of either eye entered this trial. This level of hypermetropia was chosen after a preliminary, unpublished, study of the range of refractions at 6 months had shown that approximately 9% of children have this amount of hypermetropia and that such children had a 20% chance of having some visual defect. The question of informed consent proved difficult, because many mothers could not appreciate the issues involved in their child being identified as being at risk for squint and/or amblyopia. They were therefore told their child was included in a long-term study of the possibility of preventing squint and amblyopia, but the exact details of the randomisation techniques were not explained unless requested.

Three hundred and seventy two children born between July 1978 and July 1981 entered the trial. One child was excluded because he had congenital nystagmus.

### PROTOCOL AND METHODS

All refractions were performed by the same person (RMI) at 1 metre after cycloplegia with cyclopentolate 1% instilled twice (40 minutes and 30 minutes) before retinoscopy. In order to categorise the children into their various degrees of hypermetropia a figure was derived which is recorded as the 'refraction' for each child. This figure was obtained by subtracting 1·75 D from the 1 metre retinoscopy figure in the most hypermetropic meridian. This figure is distinct from the prescription (if given), which was based on subtracting 2·00 D from each meridian of the retinoscopy. Thus, for a child with a retinoscopy of +4·00/+6·00 the 'refraction' would be +4·25 D, but the prescription would be +2·00 DS/ +2·00 D cyl axis 90°. Half of the children who had +4·00 or more D meridional hypermetropia were randomly allocated treatment with spectacles. Refraction was repeated at 1 and 3½ years, and in between if the clinical situation necessitated it – for example, if squint became manifest or if the glasses needed replacing. Observation was continued until the refraction became <+2·00 DS right and left and <+1·50 D astigmatism. If squint was detected, the child was treated on conventional lines, that is, spectacles, occlusion, operation as necessary.

An attempt was made to see the children every three months, but, as in the previous trial, attendance was irregular in some cases and reminders were sent when necessary. Fifty six children dropped out at an early stage and others as time progressed. All were recalled for assessment at age 3½.

In assessing the results we considered only two matters. The first was the presence or absence of squint as demonstrated by the cover test, and the second was the last known corrected visual acuity with spectacles if worn. Visual acuity was recorded on either the linear Sheridan-Gardiner or Snellen tests.

### COMPLIANCE WITH TREATMENT

An assessment of whether glasses were being worn was attempted and recorded each time a child attended. Some children obviously wore the glasses consistently, but it was apparent that some wore them irregularly and others not at all. The 'treated' children were therefore divided into two groups: T+ where compliance was judged (by inspection of the records) to be satisfactory and T± where it was judged to be unsatisfactory. This allocation was made before the analysis of the visual results.

## Results

Information about the presence of squint

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TABLE I *Incidence of squint*

| | | *No squint* | *Squint* | *% Squint* |
|---|---|---|---|---|
| No treatment | | 104 | 37 | 26 |
| Treatment | T+ | 53 | 17 | 24 |
| | T± | 57 | 17 | 23 |

TABLE II *Final visual acuity*

| | *6/6* | *6/9* | *6/12* | *6/18* | *6/24* | *6/36* | *6/60* |
|---|---|---|---|---|---|---|---|
| No treatment | 54 | 58 | 11 | 8 | 6 | 2 | 2 |
| Treatment | 72 | 44 | 17 | 4 | 2 | 2 | 3 |

TABLE III *Final visual acuity*

| | | *6/6* | *6/9* | *6/12* | *6/18* | *6/24* | *6/36* | *6/60* |
|---|---|---|---|---|---|---|---|---|
| No treatment | | 54 | 58 | 11 | 8 | 6 | 2 | 2 |
| Treatment | T+ | 37 | 25 | 6 | 1 | 0 | 0 | 1 |
| | T± | 35 | 19 | 11 | 3 | 2 | 2 | 2 |

TABLE IV *Final visual acuity and treatment*

| | *6/12 or better* | *6/18 or worse* |
|---|---|---|
| Treatment T+ | 68 | 2 |
| No treatment | 123 | 18 |

$\chi^2=4\cdot26$, df=1, $p<0\cdot05$.

detected by the cover test, corrected visual acuity of the 'worse' eye after all additional treatment including occlusion, compliance with the initial treatment, and the cycloplegic refraction at age 3½ is available for 285 of the 372 children who originally entered the trial. This forms the basis of the results shown above. Three of the children recorded as having squint had divergent squint and the remaining 68 had convergent squint.

Even if the children drawn for treatment are split into two subgroups according to their compliance with treatment (T+ and T±), it is clear that treatment from the age of 6 months has not altered the incidence of squint at all (Table I).

The last known acuities of the 'worse' eye of the children divided into two groups – that is, those drawn for treatment and those drawn for no treatment – are shown in Table II. A statistically significant difference cannot be identified.

If the children drawn for treatment are divided into two subgroups according to their compliance with treatment (T+ and T±), the figures in Table II become those shown in Table III.

A statistically significant difference can now be identified if the T+ group are compared with those drawn for no treatment (Table IV).

## Discussion

Abnormal hypermetropia is clearly associated with squint and amblyopia which does not respond to current methods of treatment.[2] In this study the *prescription* of spectacles from the age of 6 months did not reduce the incidence of squint (Table I), nor did it lead to a significantly improved final visual acuity after all additional treatment had been given (Table II). At present, therefore, there is no indication to screen children at the age of 6 months with a view to prescribing spectacles for those who are abnormally hypermetropic in the hope that this will reduce the incidence of squint or reduce the severity of amblyopia.

However, those children who wore their glasses consistently may have achieved a better final visual acuity than those who did not wear glasses (Table III). The evidence for this is not impressive: a significant difference depends on how the figures are arranged for statistical analysis (see Table IV). These results do no more than suggest that further research into the prevention of amblyopia, as distinct from squint, may yet prove worthwhile.

An incidental observation on this sample of children was that those whose initial hypermetropia became less by the age of 3½ had a significantly lower incidence of squint and a better last known visual acuity than those whose hypermetropia did not become reduced. This association between emmetropisation[3,4] and the visual outcome is to be explored in more detail in another paper.

We thank Mrs L Neale for many hours of secretarial and administrative work.

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# Immunoglobulins in paired specimens of vitreous and subretinal fluids from patients with rhegmatogenous retinal detachment

Geoffrey E Rose, Brenda M Billington, A H Chignell

Abstract

**Evidence suggests that there is a net movement of fluid through the retinal break in eyes with rhegmatogenous retinal detachment, this net movement being directed from the vitreous humour into the subretinal space. However, it remains uncertain how much fluid exchange occurs in *both* directions across such breaks. The concentration ratios of IgG/IgM or IgA/IgM, derived from assay of immunoglobulins in vitreous humour, subretinal fluid, and serum from a group of 19 such patients, suggest a lack of free, *two-directional*, fluid movement across the retinal break. Furthermore the IgG/IgM ratios for the two intraocular fluids were significantly greater than that of serum, this suggesting that these intraocular fluids are formed, at least in part, by a selective transudation of serum.**

The subretinal fluid from human eyes with rhegmatogenous retinal detachment contains various proteins,[1-3] and there is some evidence to suggest a plasma derivation for some components of this fluid.[2,4,5] By immunochemical methods soluble proteins from vitreous humour have been identified in human subretinal fluid.[3] The subretinal fluid also contains lipoproteins, probably derived either locally from degradation of retinal components[6] or possibly by enzymatic degradation of $\alpha_1$ lipoproteins by phospholipase A in the subretinal fluid.[7] Other investigators have proposed on cytological and biochemical evidence that subretinal fluid is derived from retinal elements, from vitreous humour, and from serum leaking from choroidal and retinal vessels.[8] If vitreous humour and subretinal fluid were derived from multiple sources and no exchange occurred across the retinal hole, the two fluids might be expected to differ (Fig 1A).

Although most evidence is compatible with a *net* movement of fluid through the retinal hole in a direction from the vitreous humour to the subretinal space (Fig 1B), there remains doubt as to the degree of mixing of the two fluids by this route. In a study of monkey eyes with long-standing rhegmatogenous retinal detachment, fluorescein isothiocyanate-dextran (molecular weight 70 000 daltons) was shown to leave the vitreous cavity by bulk flow into the subretinal space,[8] though egress from the latter space was very slow, tracer molecules still being present after six weeks.

If vitreous humour and subretinal fluid reach chemical equilibrium, either by diffusion of solutes (Fig 1C) or by a bulk, two-directional exchange of fluid (albeit with unequal flux in either direction; Fig 1D), then the two fluids should display biochemical similarity.

In order to assess the degree of identity or dissimilarity of the two fluids, we present the first reported comparison of *paired* specimens of vitreous and subretinal fluid obtained during pars plana vitrectomy for rhegmatogenous retinal detachment.

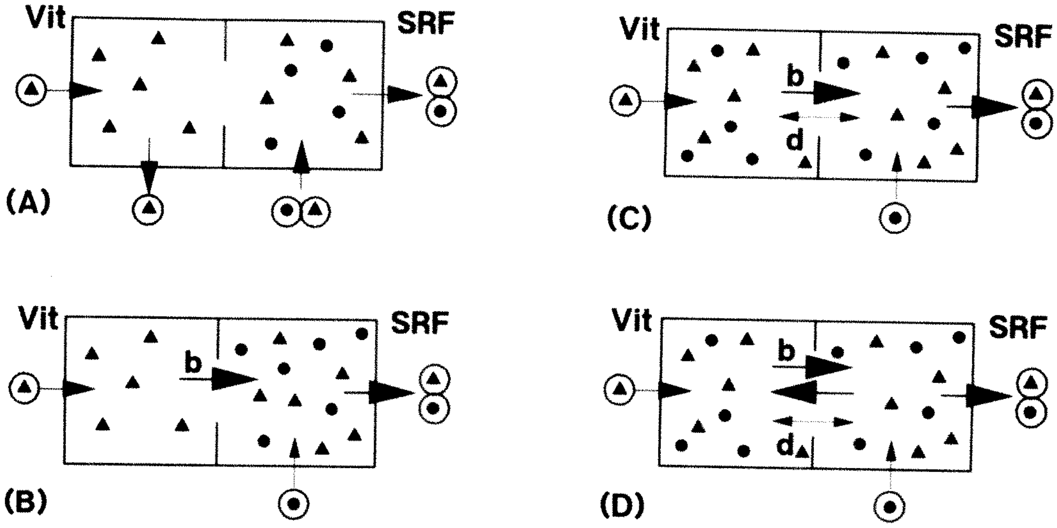

*Figure 1: Movement through the retinal holes, between the vitreous humour (Vit) and the subretinal fluid (SRF), in eyes with rhegmatogenous retinal detachment; this movement being by diffusion (d) or by bulk flow of fluid (b).*
*(A) No movement across hole; fluids in the two compartments are significantly different.*
*(B) Unidirectional bulk flow; two fluids are significantly different.*
*(C) Unidirectional bulk flow and bidirectional diffusion; two fluids are not significantly different.*
*(D) Bidirectional bulk flow and diffusion; two fluids are not significantly different.*

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TABLE I *Measured concentrations (mean, standard deviation in brackets, and range) of immunoglobulins G, A, and M (mg/l) in specimens of serum, subretinal fluid and vitreous humour from 19 patients with rhegmatogenous retinal detachment*

| | *Immunoglobulin* | | |
|---|---|---|---|
| *Type of fluid* | *G* | *A* | *M* |
| Serum | 10790 (2080)<br>7140–15500 | 2675 (957)<br>1330–4420 | 1168 (537)<br>585–2680 |
| Subretinal fluid | 1246 (1860)<br>7·6–6550<br>(11·6% (4·02%))* | 186 (283)<br>2·3–1110<br>(7·2% (2·28%))* | 29 (42)<br>3·1–162<br>(2·7% (0·90%))* |
| Vitreous fluid | 124 (118)<br>2·4–397<br>(1·2% (0·24%))* | 22 (30)<br>2·0–133<br>(0·97% (0·37%))* | 6·7 (6·3)<br>2·0–27<br>(0·69% (0·15%))* |

The vitreous humour is liable to dilutional error, the subretinal fluid specimens less so. Values marked thus * denote mean percentage of the serum concentrations (with standard error of the mean).

TABLE II *Concentration ratios (mean, standard error of mean in brackets, and range) of the lower molecular weight immunoglobulins (classes G and A) with respect to the higher molecular weight immunoglobulin M in specimens of serum, subretinal fluid, and vitreous humour*

| | *Immunoglobulin concentration ratios* | |
|---|---|---|
| *Type of fluid* | *IgG/IgM ratio* | *IgA/IgM ratio* |
| Serum | 11·0 (1·2)<br>3·2–20·1 | 2·9 (0·5)<br>0·9–7·5 |
| Subretinal fluid | 71·2 (28·2)<br>0·6–519·3 | 7·7 (2·5)<br>0·2–42·3 |
| Vitreous fluid | 22·1 (4·8)<br>0·6–68·8 | 3·0 (0·6)<br>0·3–8·9 |

Ratios are independent of any dilutional errors occurring during the collection of the specimens.

An assay of the concentrations of immunoglobulins G (molecular weight approximately 150 000 daltons), A (MW 180 000), and M (MW 900 000) was performed and the concentrations compared with those in the serum of the same patients. These molecules were chosen because of their normal presence and stability in biological fluids and their range of large molecular weights, with an assumed poor passage across intact retina.

## Patients and methods

Fourteen male and five female patients who required pars plana vitrectomy and drainage (internal or external) of subretinal fluid were selected for the study; two of the 19 were diabetic. Their ages were from 14 to 75 years (mean 52 years), and the duration of their symptoms of retinal detachment was from one to 52 weeks (mean 11 weeks). There were no cases of giant retinal tear, the largest hole being less than 6 mm in length and the maximum number of holes recorded being five. Although six of the patients had previous external buckling for retinal detachment in the same eye (three without drainage of subretinal fluid and three with drainage), this was performed at least four weeks prior to the study, a time sufficient to re-establish an equilibrium within the eye.

All patients underwent pars plana vitrectomy. The first sample from the vitreous cavity was aspirated with the Ocutome unprimed to prevent dilution of this specimen within the aspiration tube. The vitreous sample was drawn at a three-way tap system and subretinal fluid was collected either internally, by using a drainage needle passed through the retinal break, or by external drainage (collected within a syringe). When the specimens had been collected, the retinal reattachment procedure was completed by established surgical techniques.

A specimen of blood was drawn at the time of surgery and the serum separated. The three specimens for each patient were stored at 4°C until analysis. The concentrations of immunoglobulins G, A, and M (IgG, IgA, and IgM) in each of the specimens was measured by a rate nephelometric immunoassay (standard reagents, on a Beckman ICS Analyser II; Beckman Instruments, Fullerton, California).

Although every effort was made to avoid dilution of the specimens of intraocular fluids during their collection, this was not possible in all cases. This dilution renders a comparison of measured concentrations of the substances in the vitreous humour and the subretinal fluid (Table I) inaccurate, and the assayed concentrations are not considered further in this paper.

Various indices, independent of the degree of dilution, were derived to overcome the problems of dilution of the specimens during collection. These indices were based on the ratios of concentrations of smaller immunoglobulins (IgG and IgA) to those of the larger immunoglobulin M.

Similar ratios for IgG/IgM (or IgA/IgM) in paired specimens of vitreous humour and subretinal fluid would be strongly suggestive of either a common origin for, or a free two-directional mixing of, the two fluids (Figs 1C and 1D). Markedly different ratios would suggest an additional source (or sources) for one or both of the fluids as well as a lack of bidirectional mixing (Figs 1A, 1B).

## Results

The concentration ratios (dilution independent) of IgG/IgM and IgA/IgM in the three fluids are presented in Table II. There is a significant difference between the IgG/IgM ratios of serum and vitreous humour (paired Student *t* test, $p<0.05$) and between the IgG/IgM ratios of serum and subretinal fluid ($p<0.05$). The difference in concentration ratios between vitreous humour and subretinal fluid is, however, not significant. There was no significant difference between the IgA/IgM concentration ratios in vitreous humour, subretinal fluid, or serum.

Vitreous humour concentration ratios did not show a significant correlation with those of the subretinal fluids either for IgG/IgM ($r=-0.232$) or for IgA/IgM ($r=-0.256$).

There was no significant difference between the various vitreous humour or subretinal fluid concentration ratios in the six eyes with preoperative uveitis and the other 13 eyes (Table III). The IgG/IgM and IgA/IgM ratios in subretinal fluid had a significant positive linear correlation with the duration of retinal detachment ($r=0.73$, $p<0.01$ and $r=0.62$, $p<0.01$, respectively), but vitreous humour concentration ratios did not show this phenomenon. The vitreous humour or subretinal fluid concentration ratios in seven eyes with detachments of one month's duration or less were not, however, significantly different as compared with six eyes with detachments of three months' duration or longer (Table III).

TABLE III *Immunoglobulin concentration ratios (mean, standard error of mean in brackets) in two intraocular fluids, with respect to the presence of preoperative anterior uveitis or the duration of retinal detachment*

| | *Vitreous humour* | | *Subretinal fluid* | |
|---|---|---|---|---|
| | *IgG/IgM* | *IgA/IgM* | *IgG/IgM* | *IgA/IgM* |
| *Preoperative anterior uveitis* | | | | |
| Absent (13) | 23·1 (6·54) | 3·52 (0·76) | 76·3 (40·8) | 8·26 (3·50) |
| Present (6) | 19·8 (6·00) | 1·93 (0·36) | 60·4 (21·8) | 6·48 (2·34) |
| *Duration of retinal detachment* | | | | |
| <1 month (7) | 21·5 (7·26) | 2·79 (0·75) | 46·6 (18·4) | 5·31 (1·86) |
| >3 months (6) | 12·4 (6·65) | 1·35 (0·41) | 145 (83·3) | 13·2 (7·27) |

## Discussion

Experimental evidence suggests that ocular fluid dynamics in eyes with rhegmatogenous retinal detachment are abnormal. Aqueous humour production is directed posteriorly into the vitreous humour, from which space protein and fluid pass through the retinal hole into the subretinal space; fluid is pumped from this latter space by the retinal pigmentary epithelium, with sequestration of larger molecules within the subretinal space.[9] Although interpretation is complicated by the possible dilution during collection of the specimens in the present investigation, the markedly greater concentrations of immunoglobulins in subretinal fluid as compared with vitreous humour accord with this hypothesis.

The high values for the average concentration ratios of IgG/IgM in vitreous humour and subretinal fluid, both significantly different from the ratio in serum, would suggest that the two intraocular fluids gain a significant contribution either by a selective filtration of serum (with a relative restriction of the passage of the larger IgM molecule), by a selective secretion or local production of IgG within the eye, or by a selective clearance of the large IgM molecule from the eye. Although the IgG/IgM and IgA/IgM ratios in subretinal fluid increased significantly with the duration of retinal detachment, suggesting an increased leakage or a local production of IgG, it is notable that preoperative uveitis did not appear to lead to the increase in the IgG/IgM ratio of intraocular fluids that might be expected if either inflamed intraocular vessels leaked the smaller IgG molecule or there was local production of IgG within the eye.

The similar values for IgA/IgM ratios in the three fluids would suggest that somewhat different mechanisms apply to the larger IgA molecule.

On the basis of a simple comparison of average concentration ratios in vitreous humour and subretinal fluid, a common origin for the two intraocular fluids cannot be excluded because the ratios are similar. However, the *lack* of direct correlation of the ratios in the two fluids implies a 'functional barrier' to maintain such a lack of correlation. Although the lack of correlation might arise from non-representative sampling of each fluid, this is unlikely because of the relatively large samples taken at surgery. Such a functional barrier suggests that the retinal break does not allow a significant diffusion (Fig 1C) or a significant, two-directional, bulk communication (Fig 1D) of the two intraocular fluids. Viewed in the light of surgical manipulation, which can act only to increase mixing of the two fluids, this finding of a restriction of movement across the retinal break becomes even more probable. It is possible that this restrictive, functional 'barrier' exists particularly in those eyes with relatively long-standing retinal detachments, as in the present series of eyes.

Evidence from the present investigation, indicating that free mixing of fluids in the vitreous cavity and the subretinal space does not occur across the retinal hole in eyes with rhegmatogenous retinal detachment, is in agreement with the accepted hypothesis that net movement across the retinal hole occurs from the vitreous humour to the subretinal fluid (Fig 1B). Moreover, such sequestration in the two compartments would accord with the appearance of 'Schleren', passing from the subretinal into the preretinal space, when a retinal hole is disturbed during vitrectomy.

The authors gratefully acknowledge the assay of immunoglobulins performed by Professor A H S Rahi and his staff at the Institute of Ophthalmology.

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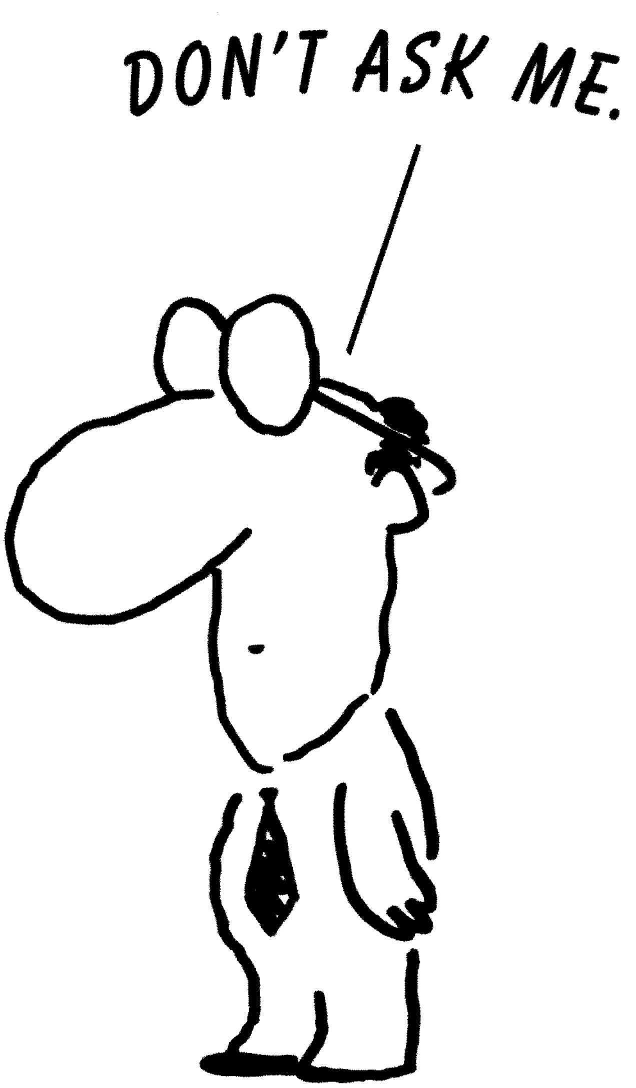

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# External ocular findings in lupus erythematosus: a clinical and immunopathological study

Peggy Frith, S M Burge, P R Millard, F Wojnarowska

## Abstract

**A selected group of 18 patients with systemic lupus erythematosus (SLE) and 30 patients with chronic cutaneous lupus erythematosus (CCLE) showed an unexpectedly high incidence of problems involving the globe or eyelids. Five SLE patients had recurrent episcleritis, two CCLE patients had lower tarsal plaques, and two further CCLE patients had erosion of the lower lid margins associated with conjunctival scarring and symblepharon. This association has not previously been reported. There was an unexpectedly high incidence of deposition of immunoreactants in a linear pattern at the basement membrane zone in normal bulbar conjunctiva, which occurred in both SLE (42%) and CCLE (50%). The significance of these findings is discussed. We believe surface ocular problems in lupus erythematosus to be under-reported and that direct immunofluorescence of bulbar conjunctival biopsy might be helpful in diagnosis.**

Lupus erythematosus (LE) is diagnosed and defined according to clinical and laboratory criteria. Patients with systemic LE (SLE) have manifestations outside the skin, and a high frequency of circulating antinuclear antibodies.[1] Patients with chronic cutaneous LE (CCLE) have scarring disease confined to the skin and rarely have circulating antinuclear antibodies.

Ulceration of the mouth is quite common in SLE, occurring in up to 45% of patients,[2 3] and is accepted as one of the clinical diagnostic criteria. Chronic oral plaques may also develop in up to 20% of patients with CCLE,[2 4] but in most the presence of characteristic skin lesions is a guide to the aetiology. In both conditions the oral lesions have similar histopathological abnormalities to those found in skin.

Direct immunofluorescence (IMF) of skin shows deposition of immunoreactants at the basement membrane zone in some patients with SLE – up to 80% in uninvolved skin[5] – and in CCLE in biopsies from skin or lip lesions.[6 7] The significance of this finding is uncertain in terms of prognosis and pathogenesis, but it may be helpful in confirming the diagnosis if other confounding disorders such as pemphigoid are excluded.

In patients with SLE reports of surface ocular abnormalities are confined to passing references to a low incidence of conjunctivitis, episcleritis, or scleritis, and assessment of the incidence of sicca.[8-11] In patients with CCLE Kaposi mentions involvement of the eyelid in his description of discoid LE in 1883.[12] Subsequent reports are sparse, describing focal tarsal conjunctival lesions,[13-15] or involvement of the lid margin,[13 14 16-20] reviewed by Huey *et al.*[18]

Our group has previously made a comparison of clinical and immunofluorescent findings in the skin, mouth, and conjunctiva in cicatricial and bullous pemphigoid.[21] In these patients, presenting with skin or mouth lesions, we found an unexpectedly high rate of asymptomatic ocular abnormalities, including positive conjunctival IMF. We were therefore interested to study a group of patients with SLE and CCLE in a similar way to see if ocular features were present even if ocular symptoms were absent.

## Patients and methods

Patients were recruited from the dermatology, rheumatology, and general medical clinics. Although they were not known to have ocular problems at presentation, there was a referral bias in favour of patients with ocular symptoms or signs. From a pool of 53 SLE and 68 CCLE patients assessed for a study of all mucosal sites 18 patients with SLE and 30 with CCLE were referred.

*Systemic LE*. Eighteen patients were considered to have SLE by American Rheumatism Association 1982 criteria; 16 were female and two male. All except one had skin and joint involvement, and eight had renal disease. Their ages ranged from 27 to 69 years (mean 46·5 years). The disease duration ranged from 9 months to 31 years (average 11·6 years). Sixteen patients were receiving immunosuppressive treatment with oral prednisolone (2·5–30 mg/day, average 9 mg), some also with azathioprine and/or antimalarials. One patient with recent presentation of an urticarial LE rash was untreated, as were two patients with mild or inactive disease.

*Chronic cutaneous LE*. Thirty patients fulfilled clinical and histopathological criteria for CCLE, and in 18 this was confined to the head and neck. Histological criteria were the presence of follicular plugging, lichenoid lymphocytic infiltrate, and basal cell liquefaction. Twenty patients were female, 10 male. Their ages ranged from 22 to 77 years (mean 47·5 years). The disease duration ranged from 2 to 54 years (mean 12·8 years). Most were controlled with topical corticosteroid and sunscreen preparations; five patients were also taking antimalarials.

*IMF control patients*. Bulbar conjunctival biopsies were obtained from 50 patients at the time of surgery for unrelated conditions such as cataract, squint, and retinal detachment. No patient had known primary conjunctival disease. Twenty six were female, 24 male, and their ages ranged from 1 to 88 years (mean 63 years).

*Clinical methods*. A detailed history of ocular

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TABLE I *Clinical ocular signs in SLE and CCLE*

| | *Systemic LE* | *Chronic cutaneous LE* |
|---|---|---|
| *No. of patients* | *18 (%)* | *30 (%)* |
| Lids | | |
| Blepharitis | 3 (17) | 5 (17) |
| Lid plaque | 0 | 2 (7) |
| Lid scarring | 0 | 2 (7) |
| Symblepharon | 0 | 2 (7) |
| Globe | | |
| Episcleritis, recurrent | 5 (28) | 0 |
| Episcleral injection, chronic | 0 | 2 (7) |
| Dryness | 2 (11) | 2 (7) |

symptoms was taken, particularly of redness of the lids or globe, soreness, discomfort, or dryness, and itching or discharge. These were graded subjectively as mild, moderate, or severe. The lid surfaces and margins and the everted conjunctival surface and globe were examined by the slit-lamp by the same ophthalmologist (PF). Schirmer's testing with standard strips for 5 minutes was recorded on a single occasion in each patient.

*Biopsies.* Biopsies were taken from consenting patients at a standard site from the upper bulbar conjunctiva, which was clinically normal and not sun-exposed. The simple technique with topical anaesthesia has been previously described.[22] Tissue snips 2 mm long were embedded in optimal cutting temperature (OCT) medium and snap frozen. The conjunctiva of 12 SLE and 21 CCLE patients was biopsied (that is, 2/3 in both groups). All patients except three also had biopsies of normal forearm skin and lip to compare the incidence of positive IMF at the three sites.

Cryostat sections were examined by direct immunofluorescence using fluorescein isothiocyanate (conjugated) (FITC) labelled antihuman IgG, A, M, C3, C4, and C1q (Hoechst UK Ltd). The assessing pathologist (PRM) was unaware of the patient's status.

The study was carried out with the informed consent of the patients and the approval of the Ethical Committee.

## Results

The clinical findings in both groups are summarised in Table I.

### SLE

Twelve patients, or two-thirds, reported ocular symptoms. Intermittent redness of one or both globes with moderate discomfort and no discharge was suggestive of recurrent episcleritis in five patients (28%). This was confirmed in each case by observation during an attack (Fig 1). One patient mentioned recurrent redness of the lids, and three patients had non-specific, non-scarring blepharitis. Three patients described itching, and three others swelling of the lids without an atopic background. Two patients, one of whom was asymptomatic, had significant dryness, with a Schirmer's test of less than 10 mm in both eyes. Thus overall nearly half the patients had signs which could have been related to the underlying SLE.

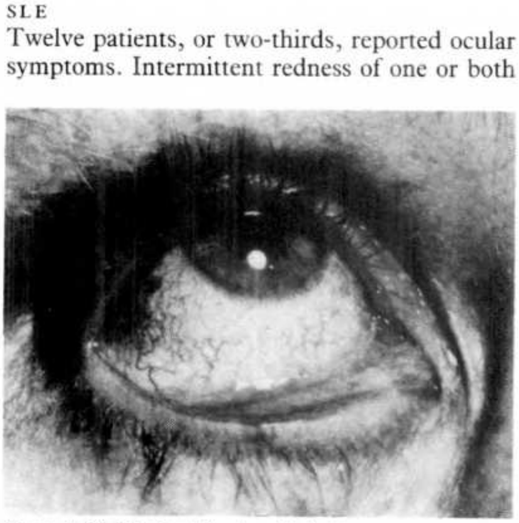

*Figure 1: SLE patient showing episcleritis.*

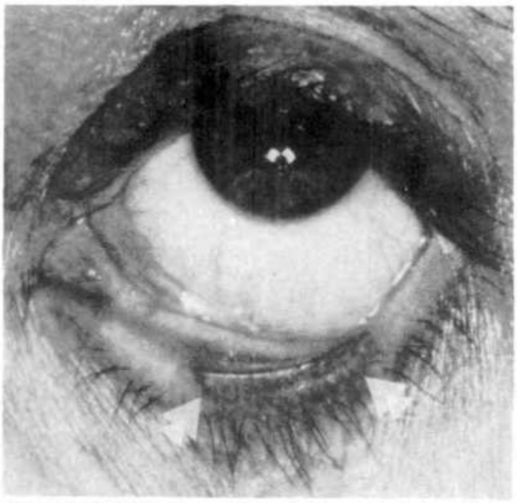

*Figure 2: CCLE patient with focal-plaque-like lesion of left lower eyelid.*

### CCLE

Seventeen patients, just over half, reported symptoms. Three reported persistent redness of the globe and 11 redness of the lids. Four mentioned itching; in one with ocular scarring this was intermittently severe.

Ten patients, or one-third, had ocular signs. In five there was non-specific blepharitis without scarring. In contrast two other patients had focal plaque-like lesions of the lower lid. These lesions were circumscribed, red, oedematous areas which involved the lid margin and extended on to the lower tarsal conjunctival surface. The lesions were bilateral in one patient, unilateral in the other (Fig 2). They responded well to topical steroid treatment, but in the patient with more extensive bilateral lesions these have recurred as treatment was reduced.

Two patients who both had CCLE of long duration (30 and 54 years) had striking lower lid involvement with pronounced scarring and tissue loss, resembling their destructive facial skin lesions. One of these patients said that her eyelids were intermittently very itchy; the other had only minor discomfort. In both patients the lids were thickened and red, with focal loss of lid margin architecture and tissue, including lash loss. There was a mild degree of ectropion in each case, but the lower puncta were open. The mucocutaneous junction was disorganised and keratinised. In addition, in both patients eversion of the lower lid showed the lower tarsal conjunctiva to be scarred, with shrinkage of the

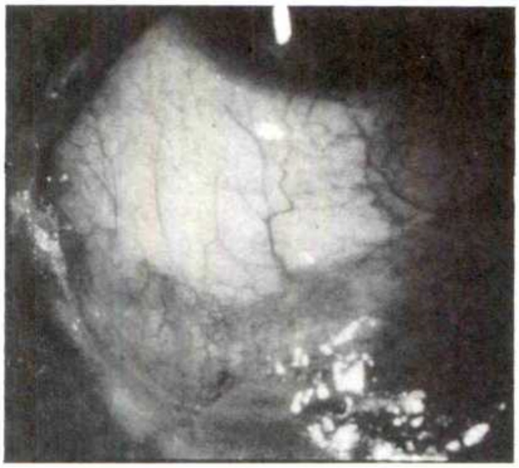

*Figure 3: CCLE patient with right lower eyelid everted, showing scarring of lid margin and lower conjunctival fornix.*

lower fornix and symblepharon formation (Fig 3). The medial canthal architecture was also lost. The upper lids were normal. The bulbar conjunctival and episcleral vessels were persistently dilated. One patient had central stromal corneal scarring with reduced vision which he attributed to trauma in childhood, but otherwise the corneae were normal. Two patients gave reduced results in Schirmer's test.

### CONJUNCTIVAL IMMUNOFLUORESCENCE

Twelve, that is two-thirds, of the SLE patients had conjunctival biopsy. Five biopsies showed a linear pattern of immunoreactants deposited at the basement membrane zone (42%). In four cases this was IgG alone (Fig 4), in the other C1q alone.

Twenty-one, also two-thirds, of the patients with CCLE were biopsied and 10 (48%) showed an identical linear pattern in the conjunctiva. All had IgG, and one, a patient who had symblepharon, also had linear IgA and C3.

In neither group was there correlation between clinical and IMF findings, many IMF positive patients having no significant symptoms or signs. Of SLE patients with episcleritis two did and two did not have immune deposits, and one was not biopsied. Both CCLE patients with scarring had positive linear IMF.

A comparison of positive IMF in skin and in lip mucosa in the same patients (Tables II and III) showed that in both SLE and CCLE the rate of IMF positivity was highest in conjunctiva compared with skin and lip, particularly in CCLE.

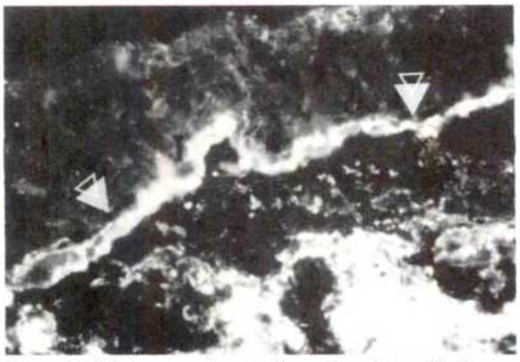

*Figure 4: SLE patient showing linear deposition of IgG at basement membrane zone in conjunctiva.*

TABLE II *Systemic LE: tissue immunofluorescence at three uninvolved sites*

| | *Conjunctiva* | *Skin* | *Lip mucosa* |
|---|---|---|---|
| Total no. biopsies | 12 | 16 | 16 |
| No. positive band | 5 | 5 | 4 |
| % Positive band | 42 | 31 | 25 |

TABLE III *Chronic cutaneous LE: tissue immunofluorescence at three uninvolved sites*

| | *Conjunctiva* | *Skin* | *Lip mucosa* |
|---|---|---|---|
| Total no. biopsies | 21 | 30 | 29 |
| No. positive band | 10 | 1 | 1 |
| % Positive band | 48 | 3 | 3 |

In control patients a positive linear result was found in five of 50 conjunctival biopsies. One patient had had a renal transplant and could reasonably be excluded, as the immune deposits might have been related to the underlying condition. Another positive control patient, included in analysis, had thyroid eye disease. Thus in three of 49 control patients (6%) linear IgG was present, and in a further patient linear IgM.

## Discussion

This study of the prevalence of clinical and immunopathological abnormalities of the ocular surface in LE has shown a surprisingly high rate in both systemic and chronic cutaneous LE.

### CLINICAL FEATURES

Previous reports date from 1907. The first report in English[13] (1932) describes three patients with conjunctival lesions and reviews reports of nine other patients, three with conjunctiva, four with lid, and two with both sites involved. Since then there have been occasional reports totalling eight patients with conjunctival[14 15] and 29 with lid[14 16-20] lesions thought to be related to associated lupus. It is not always possible to be sure if these are cases of SLE or CCLE.

Five patients showed swelling of the lids associated with lupus profundus, and panniculitis was shown on facial skin biopsy.[17] Otherwise lid lesions were characterised by blepharitis with scaling, madarosis, and non-contractile scarring in some cases. Biopsy of the lid margin in four cases[18 20] showed a similar histology to LE skin lesions elsewhere, with follicular plugging, oedema, basal cell liquefaction, and a dense, patchy, cellular infiltrate. The lesions were distinguished clinically from chronic blepharitis by the association with skin lesions of LE in all but three cases, and there was often a history of exacerbation by sunlight. In three cases[20] the lid lesions were the only abnormality but proved to be typical of CCLE on biopsy.

Conjunctival lesions have been described as circumscribed, red, oedematous, velvety areas on the upper or lower tarsal surface, which heal spontaneously or in response to systemic treatment, sometimes leaving atrophic depressed scars.[14 15]

We consider that in our group of SLE patients that recurrent episcleritis in five out of 18 (28%)

is likely to be related to the underlying LE. One patient presented with red eyes as her first manifestation, progressing within months to joint and urticarial skin involvement with positive antinuclear antibodies and characteristic skin histopathology. Her eyes tended to flare with her systemic disease, but subsided with increase in systemic and topical treatment. It is reasonable to consider this a manifestation of an immune complex disorder, though circulating complexes were not measured in our patients. We cannot prove an association, but a rate of 28% seems higher than expected by chance even with a referral bias in favour of ocular problems. In this small group we did not find scleritis, which has been occasionally reported in SLE.[23]

In the CCLE group five patients (17%) had blepharitis with no special features, and this could be an incidental finding. However, a further four patients had lid involvement characteristic of the condition, though lid biopsies were not performed. Two of these patients had circumscribed plaque-like blepharitis of the lower lid margin, extending inwards on to the tarsal surface, with striking redness of the lesions well demarcated from the adjacent normal tissue. These responded rapidly to topical corticosteroid application, leaving no scars, but in one patient the lesions recurred. In one of these patients a single asymptomatic eyelid lesion was associated with marked oral involvement, and a careful search showed small plaques of CCLE behind one ear. The diagnosis of LE was made by positive linear IMF in oral tissue. Thus the lid lesion was helpful in suggesting the diagnosis.

Two further patients with CCLE had ocular findings which have not previously been described and which were strikingly similar to each other. Both patients had very long-standing facial cutaneous disease with photosensitivity, and both showed striking loss of lower lid tissue with scarring. The scarring also involved the lower tarsal conjunctiva, with symblepharon formation. This feature resembled cicatricial pemphigoid (CP), though lid margin involvement has not been reported in CP, and we believe this to be the first report of symblepharon in CCLE.

Clinical features in non-ocular mucosal surfaces in a group of 121 LE patients from which the present study was drawn are being reported separately.[24] Oral lesions were found in 10%, nasal mucosal lesions in 6% overall, and vulval lesions in 5% of the female patients.

## TISSUE IMMUNOFLUORESCENCE

There are no previous reports of tissue direct immunofluorescence findings in cases with ocular involvement, except for a single case with biopsy of oedematous lid skin which showed positive linear IgG deposition in a broad granular pattern.[19] This is the pattern found in up to 60% of patients with cutaneous LE, known as the 'lupus band'. We did not investigate IMF in eyelid skin.

Conjunctival IMF findings in LE patients have not to our knowledge been previously described. Our findings of IMF in three different tissue sites are summarised (Tables II and III) and have been reported separately.[25] We were surprised by the high incidence of conjunctival linear immunodeposits compared with uninvolved skin and lip in the same patients. We have previously found the same pattern in pemphigoid patients.[21] The comparison is particularly striking in our CCLE group, in which immunodeposits in uninvolved skin and lip were rare but were found in 48% of uninvolved bulbar conjunctiva. Perhaps circulating antibodies are bound more readily to conjunctiva or are cleared less rapidly from it.

The origin and significance of the immunodeposits at any site is unclear. Elution studies in man[26] suggest that in skin the antibody has anti-nDNA specificity, and studies in mice[27] and in humans[6] that they are related to circulating nDNA levels. It has been postulated that in-situ complexes form as nDNA is released from degenerating surface keratinocyte nuclei, perhaps particularly in response to solar irradiation,[28] but our finding of a band in non-keratinised, non-sun-exposed conjunctiva suggests other mechanisms may be involved.

In oral mucosa, linear IgG in lesional tissue is a good discriminator for LE. In a large series[7] a positive band was detected in 73% of CCLE and 100% of SLE associated lesions, but was absent from lesions of lichen planus or leucoplakia. In our large control group we found a low (6%) incidence of linear IgG in normal bulbar conjunctiva, suggesting that the association of this pattern with both SLE and CCLE is significant.

We conclude that ocular surface disorders such as episcleritis in SLE and lid and conjunctival lesions in CCLE are not uncommon, and may be under-reported, particularly as symptoms may be minor or absent. The ocular features can occur early, and may be sufficiently characteristic to suggest the diagnosis of LE. Positive linear IMF in uninvolved bulbar conjunctiva is surprisingly common in both SLE and CCLE, and this finding deserves further study, as it may be of value diagnostically. The association of CCLE with symblepharon is a new finding, and raises interesting comparisons with cicatricial pemphigoid and questions about pathogenesis of autoimmune disorders involving the basement membrane zone.

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# Corneal oxygenation: blink frequency as a variable in rigid contact lens wear

Barbara A Fink, Richard M Hill, Leo G Carney

**Abstract**

**Using a micropolarographic system, we measured the responses of six human corneas to nine oxygen exposure conditions: to air (continuous open-eye) with no contact lens in place, and to eight interblink intervals (1, 2, 3, 4, 5, 6, 7, and 300 s durations) with an oxygen impermeable lens in place. The corneal oxygen uptake rates immediately following each of those conditions were direct indices of tear bulk-flow exchange under a rigid contact lens as an oxygen route. Greatest efficiencies in reducing corneal oxygen demand were associated with the two highest blink frequencies examined (namely, for interblink intervals of 2 s or less). Even at those frequencies oxygen demands ranging from 4 to 6 times the open-eye, non-wearing, baseline rate for each eye typically occurred, clearly justifying the need for a supplementary oxygenation route, for example, directly through rigid contact lens materials having inherently high oxygen permeabilities.**

Adequate exchange between the post-lens tear reservoir and outer tear pool of the eye is vital to the physiology of the cornea during rigid contact lens wear. This exchange is required for the efficient clearance of particulate debris such as tear protein coagulates and desquamated epithelial cells and, in particular in the case of extended wear, the restabilisation of the physical characteristics of the post-lens tear reservoir (pH, osmolality, buffering capacity) on awakening. This is dependent, in time course and relative completeness, on tear bulk-flow efficiency.[1 2] In addition, access and elimination of gases (Oxygen influx and carbon dioxide efflux) across the anterior corneal surface must take place at acceptable rates.[3 4] Even the most advanced rigid gas permeable lenses fall short of providing the oxygen levels available to the cornea across its tear-epithelial interface during non-wearing, open-eye conditions.

In this study the role of blink frequency in the oxygenation of the cornea via tear bulk-flow during rigid contact lens wear was evaluated. The measurements could also serve as an index to other exchanges associated with rigid contact lens systems, which are directly dependent upon, or are influenced by, bulk-flow movement of tears as well.[5-7]

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## Materials and methods

A Clark type micropolarographic electrode was used to measure oxygen uptake rates of the cornea.[3 8 9] The electrode consisted of a platinum cathode, 25 µm in diameter, and a silver anode, 500 µm in diameter, covered with a polyethylene membrane (12·5 µm thick). Calibration of the sensor was achieved by immersing it in air and nitrogen saturated water baths, maintained at 36°C. When the probe was applied directly to the cornea, the polyethylene membrane served as a small reservoir of oxygen for the cornea. The depletion of oxygen from the membrane during contact with the cornea results in a reduced current output from the electrode. The slope value of the reservoir emptying course (that is number of seconds for the reservoir oxygen tension to descend from 140 mmHg to 40 mmHg, minus the time constant of the reservoir probe-recorder system) was used as a quantitative measure of the corneal response to each condition investigated.[8] Oxygen deprivation of the cornea was manifested as an increased probe reservoir depletion rate (that is, higher mmHg/s rate values). Fluorescein examination following probe contact revealed no damage due to the light but steady contact required.

Measurements were made on the right cornea of each of six healthy young subjects (average age: 24 years) after each of three conditions: in the normal open-eye, after the contact lens had been worn under static (non-blinking) conditions for 5 minutes (which is more than 2·5 times the period required to achieve steady state conditions),[10] and after the contact lens had been worn under dynamic (with blinking) conditions for 5 minutes. The inter-blink intervals used for the dynamic wearing conditions were 1, 2, 3, 4, 5, 6 and 7 seconds. Responses to each of the conditions, expressed as probe reservoir oxygen depletion rates in mmHg/s, were measured eight times for each cornea. All lenses were made of oxygen impermeable polymethylmethacrylate (PMMA) to eliminate the alternative (transmissivity) oxygen route to the cornea, and were designed so that the back central radius of each matched the

TABLE I *Subject, corneal, and contact lens characteristics*

| *Subject* | *Age (yr)* | *Sex* | *Corneal curvature (D, degrees)* | *Net corneal toxicity (D, axis, degrees)* | *Palpebral aperature† (mm)* |
|---|---|---|---|---|---|
| 1 | 24 | M | 42·50, 007*<br>43·12, 097 | −0·67, axis 007 | 12 |
| 2 | 25 | F | 41·62, 002<br>42·37, 092 | −0·75, axis 002 | 11·5 |
| 3 | 23 | M | 42·50, 180<br>43·47, 090 | −0·87, axis 180 | 10·0 |
| 4 | 28 | F | 41·87, 180<br>42·75, 090 | −0·87, axis 180 | 8·5 |
| 5 | 23 | M | 43·87, 180<br>44·25, 090 | −0·37, axis 180 | 10·0 |
| 6 | 24 | M | 41·37, 179<br>42·37, 089 | −1·00, axis 179 | 11·0 |

*All lenses were of oxygen impermeable polymethylmethacrylate and were of uniform design except that the back central radius of each lens was made equal in curvature to the flattest meridian of the particular cornea fitted; overall diameter=8·80 mm; optic zone diameter=7·40 mm; axial edge lift=0·09 mm; centre thickness=0·14 mm, and back vertex power=−3·00 D.
†Maximum vertical extent.

TABLE II *Oxygen uptake rates (mmHg/s) of six human corneas immediately following normal open-eye (no lens) conditions, and eight lens wearing (different inter-blink interval) conditions**

| | | *No lens condition (open eye)* | *Lens wearing conditions (seconds between blinks)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Subject* | | | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *300* |
| *Column:* | | *A* | *B* | *C* | *D* | *E* | *F* | *G* | *H* | *I* |
| 1 | x | 4·17 | 12·96 | 18·06 | 19·75 | 21·38 | 22·70 | 23·25 | 24·72 | 29·47 |
| | SD | 0·36 | 2·74 | 3·00 | 3·06 | 5·58 | 3·86 | 4·35 | 4·31 | 5·38 |
| | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 2 | x | 4·30 | 16·28 | 22·43 | 24·56 | 26·70 | 27·04 | 26·56 | 27·98 | 34·24 |
| | SD | 0·31 | 4·59 | 3·92 | 2·16 | 3·28 | 2·89 | 3·10 | 2·63 | 3·06 |
| | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 3 | x | 5·22 | 21·82 | 27·12 | 26·57 | 27·90 | 30·36 | 29·32 | 29·16 | 31·68 |
| | SD | 0·69 | 3·81 | 2·65 | 2·53 | 4·27 | 2·66 | 1·70 | 1·20 | 1·89 |
| | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 4 | x | 4·12 | 18·09 | 20·74 | 20·33 | 21·97 | 23·55 | 24·00 | 24·37 | 24·97 |
| | SD | 0·27 | 3·23 | 4·43 | 1·22 | 1·66 | 2·58 | 3·75 | 2·97 | 4·19 |
| | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 5 | x | 4·59 | 23·91 | 26·58 | 27·23 | 26·64 | 27·21 | 28·46 | 27·22 | 30·22 |
| | SD | 0·51 | 2·67 | 3·88 | 4·45 | 3·07 | 4·65 | 3·38 | 3·85 | 4·11 |
| | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 6 | x | 4·64 | 14·74 | 18·97 | 20·08 | 20·70 | 21·44 | 22·20 | 23·09 | 24·56 |
| | SD | 0·58 | 3·87 | 3·28 | 1·55 | 2·13 | 1·35 | 1·07 | 1·64 | 2·03 |
| | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Population: | x | 4·51 | 17·96 | 22·32 | 23·10 | 24·22 | 25·38 | 25·63 | 26·09 | 29·19 |
| | SD | 0·59 | 5·13 | 4·89 | 4·09 | 4·49 | 4·32 | 3·99 | 3·57 | 4·93 |
| | n | 48 | 48 | 48 | 48 | 48 | 48 | 48 | 48 | 48 |

*All lenses were of oxygen impermeable polymethylmethacrylate (PMMA) material.

flattest meridian of the cornea on to which it was fitted. In all other ways the lenses were of identical design. Table I gives the subject, cornea, and lens parameters for the study.

## Results

Table II gives, in absolute units, the oxygen uptake values (in probe reservoir depletion rates, mmHg/s) observed for the six corneas for the normal open-eye and immediately following the static wearing condition and seven dynamic wearing conditions. It can be seen that the rates of oxygen uptake which the cornea showed when released from the oppressive effect of the contact lens increased as the inter-blink intervals became longer and they were at a maximum after static wear of the contact lens. The mean uptake rate and standard deviation found for each condition are given (Fig 1) for each subject and for the combined data from all subjects (that is, the composite population based on a total of 48 measurements for each of the nine conditions).

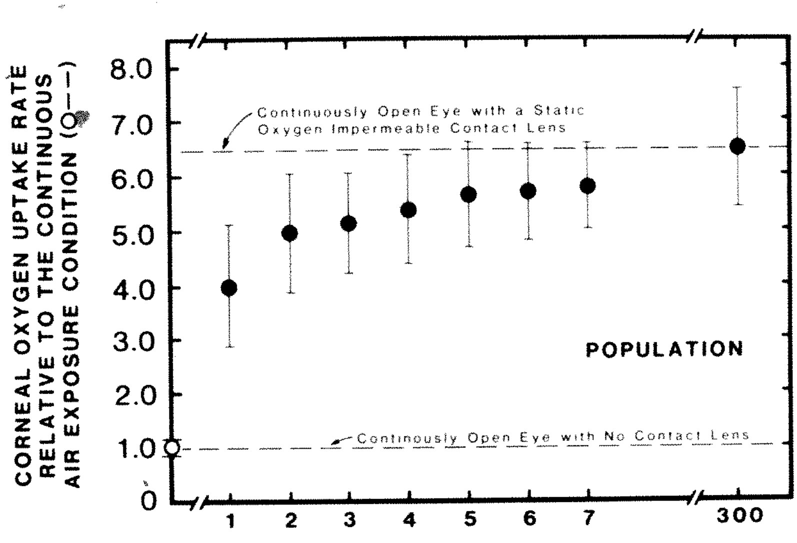

*Figure 1: The mean corneal oxygen uptake rates of six human eyes, relative to the mean non-wearing open-eye condition (1·0, open point), associated with each of eight lens wearing blink series of inter-blink intervals ranging from 1 to 7, and 300 seconds (closed points). The lenses (polymethylmethacrylate) at the thickness used (0·14 mm) permitted negligible oxygen passage through the material itself. Each point is the mean of 48 measurements, eight on each of the six corneas represented. One standard deviation above and below each mean is indicated.*

Figure 2 compares the difference in oxygen demand observed for each of these six corneas relative to the mean performance of the composite population over that spectrum of inter-blink intervals from 1 to 300 seconds.

Figure 3 summarises those ranges of inter-blink intervals over which corneal oxygen uptake values following each experimental condition were not found to be significantly different from each other by the Fisher least significant difference test[11] ($p=0·05$) within the population model shown in Figure 1.

Table III is the summary of correlations found between the non-stress baseline values from column A of Table II versus each of the inter-blink interval responses, seen in columns B through H for each subject. Also shown are the parallel correlation values for each subject between their inter-blink interval responses, columns B through H, and their responses to the maximum stress condition, column I of Table II.

## Discussion

As can be seen in Table II, a range of oxygen demands exists among individual corneas. The probe reservoir depletion rates observed here for the non-lens-wearing open-eye condition extended from a high of 5·22 mmHg/s (subject 3) to a low of 4·12 mmHg/s (subject 4). The most demanding cornea thus displayed a rate which was 27% greater than that of the least demanding under normal open-eye conditions. The presence of a range of demand among corneas is in agreement with earlier reports.[12]

Corneas also differed in the maximum oxygen uptake rates they displayed, which in all cases were found after the static lens-wearing conditions. The highest mean rate was 34·24 mmHg/s, observed for subject 2. This represented a nearly 8 times increase over the non-stress (normal, open-eye) demand level found for that same cornea. In contrast, the cornea of subject 6 showed a maximum mean rate of 24·56 mmHg/s, or an increase of only 5·3 times that same cornea's open-eye mean uptake rate. This inter-subject variability was statistically significant (ANOVA, $F_{5431}=9·74$, $p<0·001$). Subsequent post-hoc comparisons showed that subjects 1, 4, and 6 were statistically different in their overall demand profiles from subjects 2, 3, and 5.

In Table III correlation coefficients (and their statistical significance) between oxygen uptake rates are given, firstly, for the non-stress (no lens, open-eye) condition and that following lens wear at each inter-blink interval from 1 to 7 seconds (48 data pairs per correlation value); and, secondly, for the maximum stress (static contact lens wear for 300 seconds) condition and that for each inter-blink interval (also 48 data pairs). These results show that the maximum stress responses of these corneas were more highly predictive of an overall inter-blink demand profile greater or less than the population average than were the non-stress, open-eye (baseline) demand levels.

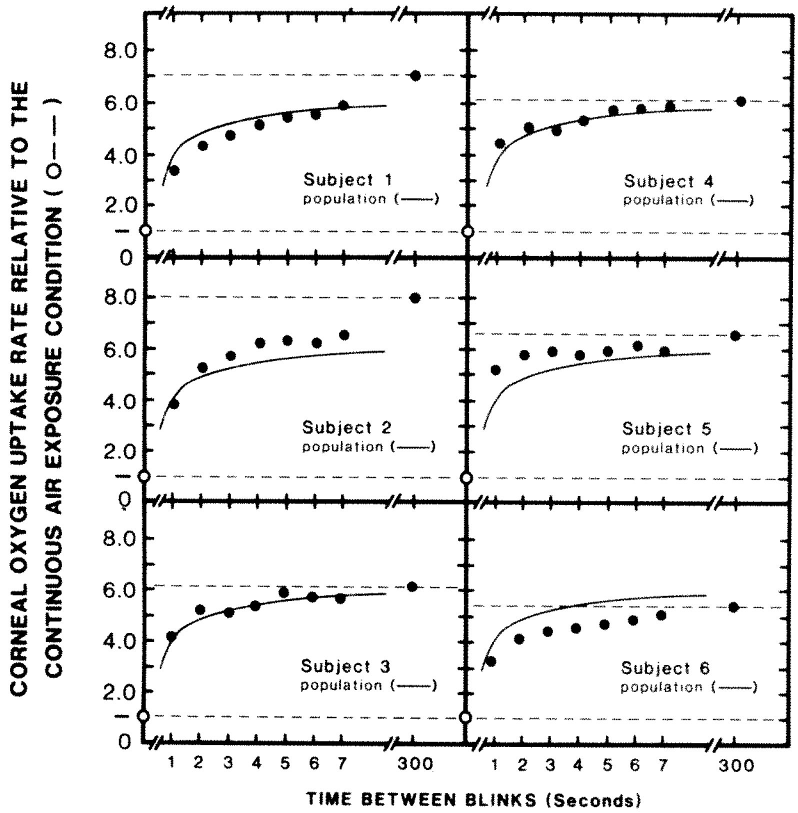

*Figure 2: A comparative summary for each of six human corneas, showing their individual oxygen uptake rates associated with each of eight lens-wearing inter-blink intervals (ranging from 1 to 7, and 300 seconds (closed points)), relative to the non-lens-wearing open-eye demand for the population (1·0, open point). The best fitted curve of mean responses for the entire population (based on the closed point means in Fig 1) is shown in each frame as well. Each closed point is the mean of eight measurements; the open point is the mean of 48 measurements. The lower dashed lines represent the relativised oxygen uptake rates for the continuously open eye with no contact lens in place for each subject. The upper dashed lines similarly represent the relativised oxygen uptake rates for the continuously open eye with a static oxygen impermeable contact lens in place.*

The demand profiles of each eye-lens system, and consequently of the composite model resulting, were found to be most sensitive to alteration at the short blink interval end of that spectrum, with increasing blink frequency resulting in lower oxygen demand following contact lens wear. Inter-blink intervals of 2 seconds or longer, however, were found to produce more gradual increases in demand, the performance levels over increasingly wider ranges of intervals not being found significantly different from one another (Fig 3). Corneal oxygen demand then is relatively insensitive to an increase of the inter-blink period beyond the population average of about 4·78 seconds.[13] Conversely, a decreasing inter-blink period below that average can significantly diminish the resultant corneal oxygen demand, making clinical attention to adequacy of blink action of importance, particularly for physiologically marginal tear exchange cases.

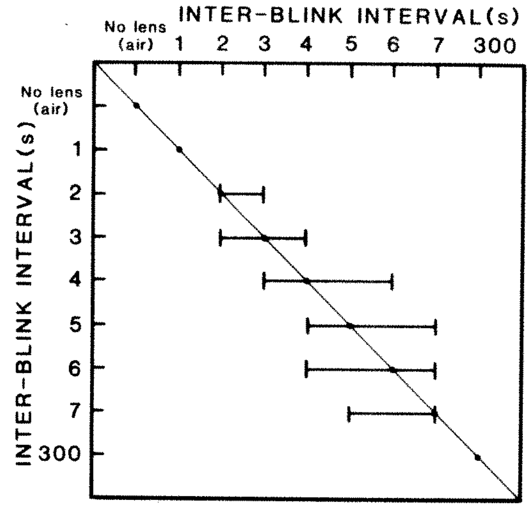

*Figure 3: Results of Fisher's least significant difference multiple comparison tests for significant differences among pairs of mean responses (population values from Table I) to nine corneal exposure conditions, ranging from no lens present and the eye continuously exposed to air (approximately 155 mmHg $PO_2$), through interblink intervals with an oxygen impermeable lens in place of 1 to 7 seconds, and for 300 seconds (that is, with the lens remaining statically on the open eye surface without a blink over those periods). At each inter-blink interval any two means not covered by the same line segment are significantly different.*

TABLE III *Correlation between oxygen demands following contact lens wear with inter-blink intervals from 1 to 7 seconds, and the two limiting conditions of non-stress* and maximum stress.†*

| Inter-blink Interval (seconds) | Non-stress, open eye | | Maximum stress, static lens wear | |
|---|---|---|---|---|
| | Correlation coefficient | Significance | Correlation coefficient | Significance |
| 1 | 0·324 | 0·024 | 0·251 | 0·082 |
| 2 | 0·339 | 0·018 | 0·491 | <0·001 |
| 3 | 0·483 | 0·001 | 0·611 | <0·001 |
| 4 | 0·419 | 0·003 | 0·589 | <0·001 |
| 5 | 0·494 | <0·001 | 0·706 | <0·001 |
| 6 | 0·415 | 0·003 | 0·684 | <0·001 |
| 7 | 0·373 | 0·009 | 0·747 | <0·001 |

*Contributing response values to the means in columns B through H of Table II versus those values contributing to the means in column I, for each of the six subjects. †Contributing response values to the means in columns B through H of Table II versus those values contributing to the means in column I, for each of the six subjects.

Tear bulk-flow exchange as an oxygen route to the cornea under rigid contact lenses is, as expected, most efficient at the higher blink frequencies (that is, for inter-blink intervals of 2 seconds or less). Nevertheless, while corneal oxygen demands associated with inter-blink intervals of 2 through 7 seconds were all found to be significantly different from those for the static (no blinks for 300 seconds) wearing case (Fig 3), they were still typically 4 to 6 times greater than the normal open-eye (non-wearing) baseline demands observed.

Corneal oxygenation during rigid contact lens wear can be maximised by three strategies now in common practice: (1) the use of comfortable but mobile lens designs; (2) the encouragement of highest blink frequencies (that is, shortest inter-blink intervals); and (3) the provision of a supplementary route for oxygen to the cornea through the use of oxygen permeable materials in rigid lenses. While such materials, with the exception of pure silicone elastomer, do not as yet have oxygen transmissivities to return corneal oxygen demands to non-wearing levels, the reduction in corneal swelling, already well substantiated in their use, clearly indicates the value of that supplementary route.[1 14 15]

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# Risk factors for proliferative sickle retinopathy

Peter D Fox, David T Dunn, Joanne S Morris, Graham R Serjeant

**Abstract**

**The prevalence, incidence, and risk factors associated with proliferative sickle retinopathy (PSR) were investigated in 786 patients with homozygous sickle cell (SS) disease and 533 patients with sickle cell haemoglobin C (SC) disease. PSR was more common in SC disease, in which there was a significant predominance of males, and it increased with age in both genotypes. In SC disease the risk of developing PSR was highest between 15 and 24 years in males, between 20 and 39 years in females, and in SS disease between 25 and 39 years in both sexes. PSR tended to be bilateral, especially in SC disease. There was no evidence of familial clustering of PSR in SC siblings, and insufficient numbers of SS siblings were available to test for clustering. Haematological risk factors associated with PSR in SS disease were a high haemoglobin in males and a low fetal haemoglobin in both sexes and in SC disease, a high mean cell volume, and a low fetal haemoglobin in females.**

Proliferative sickle retinopathy (PSR) is the major sight threatening complication in sickle cell eye disease, and may reach frequencies as high as 70% in patients with sickle cell haemoglobin C (SC) disease. The risk factors for its development are still largely unknown, partly because detailed ocular information has not been available in sickle cell populations large enough to allow comprehensive statistical analysis. A study of 261 patients with homozygous sickle cell (SS) disease including 29 with PSR noted that male patients with PSR had significantly higher total haemoglobin (Hb) and lower fetal haemoglobin (HbF) but that no correlations occurred in females.[1] Another study of 243 patients with SC disease including 90 with PSR found significant correlations of PSR with low HbF in both sexes and with a high mean cell volume (MCV) in males.[2] Since those earlier Jamaican reports 333 cases of PSR including 112 incident cases have been observed. This larger group has enabled more detailed analyses on prevalence, incidence, familial clustering, and haematological risk factors. The results of these analyses are now presented.

## Patients and methods

The patients attended the Sickle Cell Clinic at the University of the West Indies. All SS and SC patients examined between August 1970 and October 1988 were included in this study, though children in a cohort study from birth[3] were excluded. Ocular examination included visual acuities, fundal examination through dilated pupils, and fluorescein angiography where indicated. Patients were classified as having PSR regardless of whether or not the lesions were perfused when examined.

The patient's age and PSR status for the prevalence analysis was defined at the first eye examination. As patients with proliferative disease were reviewed more frequently, using age at last visit would have exaggerated the prevalence of PSR. Therefore all cases of PSR that developed during the study were excluded from the prevalence analysis. The exact age at onset of PSR was rarely available, and for the incidence analysis it was assumed that PSR developed at the mid point between the last negative and the first positive examination. Patients were divided into the following age groups for analysis: 0–9 years, 10–14, 15–19, 20–24, 25–29, 30–39, and 40 years and above.

The diagnosis of SS and SC disease was based on standard criteria.[4] Haemoglobin, red cell indices, and platelets were measured in electronic counters (Coulter ZBI6 or S plus 4, Coulter Electronics), fetal haemoglobin (HbF) by an alkali denaturation method,[5] bilirubin by the method of Lathe and Ruthven,[6] and serum iron by the method of Beale *et al.*[7] Mean cell haemoglobin concentration (MCHC) was derived from the spun microhaematocrit. $\alpha$ Thalassaemia status was determined by restriction endonuclease analysis of DNA obtained from the buffy coat.[8]

For comparison of haematological indices in patients with and without PSR at their last examination, levels were derived from the mean of multiple steady state observations. This study was confined to a subset of 1181 patients (740 SS, 441 SC) for whom complete haematological data were available. Indices with skewed distributions (HbF, bilirubin) were logarithmically transformed ($\log_{10}$ [HbF+1], $\log_{10}$ bilirubin) to give more normal distributions prior to statistical analysis. Simple comparison of the distribution of haematological indices between patients with and without PSR can be misleading, as certain indices are interdependent and age related, so multiple logistic regression analysis[9] was also used, separately for both sexes and genotypes. This approach assessed the effect of a factor assuming all other factors in the model were fixed and allowed for age related trends. Haematological indices that appeared to influence the simple comparison by Student's $t$ test were included in the logistic regression. Comparison of proportions across age groups was performed by the Mantel-Haenszel test, and a log linear regression model was used to analyse age related trends in incidence.

## Results

A total of 786 SS and 533 SC patients were examined, representing 29% of all SS patients and 55% of all SC patients registered at the clinic.

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TABLE I *Prevalence of proliferative sickle retinopathy at first examination by sex and age in 786 SS patients*

| | *Males* | | | *Females* | | | *Both sexes* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Pts with PSR* | | | *Pts with PSR* | | | *Pts with PSR* | |
| *Age group (years)* | *Patients examined* | *No.* | *(%)* | *Patients examined* | *No.* | *(%)* | *Patients examined* | *No.* | *(%)* |
| 0–9 | 8 | 0 | (0) | 9 | 0 | (0) | 17 | 0 | (0) |
| 10–14 | 38 | 0 | (0) | 42 | 0 | (0) | 80 | 0 | (0) |
| 15–19 | 68 | 2 | (3) | 99 | 1 | (1) | 167 | 3 | (2) |
| 20–24 | 72 | 3 | (4) | 98 | 2 | (2) | 170 | 5 | (3) |
| 25–29 | 46 | 2 | (4) | 61 | 4 | (7) | 107 | 6 | (6) |
| 30–39 | 55 | 14 | (25) | 79 | 9 | (11) | 134 | 23 | (17) |
| 40 plus | 41 | 4 | (10) | 70 | 8 | (11) | 111 | 12 | (11) |
| Total | 328 | 25 | (8%) | 458 | 24 | (5%) | 786 | 49 | (6%) |

TABLE II *Prevalence of proliferative sickle retinopathy at first examination by sex and age in 533 SC patients*

| | *Males* | | | *Females* | | | *Both sexes* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Pts with PSR* | | | *Pts with PSR* | | | *Pts with PSR* | |
| *Age group (years)* | *Patients examined* | *No.* | *(%)* | *Patients examined* | *No.* | *(%)* | *Patients examined* | *No.* | *(%)* |
| 0–9 | 26 | 0 | (0) | 21 | 0 | (0) | 47 | 0 | (0) |
| 10–14 | 36 | 2 | (6) | 41 | 3 | (7) | 77 | 5 | (6) |
| 15–19 | 49 | 9 | (18) | 68 | 7 | (10) | 117 | 16 | (14) |
| 20–24 | 33 | 14 | (42) | 48 | 8 | (17) | 81 | 22 | (27) |
| 25–29 | 32 | 25 | (78) | 35 | 15 | (43) | 67 | 40 | (60) |
| 30–39 | 44 | 30 | (68) | 44 | 20 | (45) | 88 | 50 | (57) |
| 40 plus | 26 | 18 | (69) | 30 | 21 | (70) | 56 | 39 | (70) |
| Total | 246 | 98 | (40%) | 287 | 74 | (30%) | 533 | 172 | (32%) |

TABLE III *Incidence rates for first development of proliferative sickle retinopathy in 41 SS patients*

| | *Males* | | | *Females* | | | *Both sexes* |
|---|---|---|---|---|---|---|---|
| *Age group (years)* | *New PSR* | *Pt.-years observation* | *Incidence (per 100 pt.-years)* | *New PSR* | *Pt.-years observation* | *Incidence (per 100 pt.-years)* | *Incidence (per 100 pt.-years)* |
| 0–9 | 0 | 2 | 0·0 | 0 | 1 | 0·0 | 0·0 |
| 10–14 | 0 | 31 | 0·0 | 0 | 63 | 0·0 | 0·0 |
| 15–19 | 2 | 110 | 1·8 | 2 | 157 | 1·3 | 1·5 |
| 20–24 | 2 | 131 | 1·5 | 2 | 167 | 1·2 | 1·3 |
| 25–29 | 3 | 124 | 2·4 | 4 | 160 | 2·5 | 2·5 |
| 30–39 | 4 | 150 | 2·7 | 6 | 219 | 2·7 | 2·7 |
| 40 plus | 5 | 256 | 2·0 | 11 | 378 | 2·9 | 2·5 |
| Total | 16 | 804 | 2·0 | 25 | 1145 | 2·2 | 2·1 |

TABLE IV *Incidence rates for first development of proliferative sickle retinopathy in 71 SC patients*

| | *Males* | | | *Females* | | | *Both sexes* |
|---|---|---|---|---|---|---|---|
| *Age group (years)* | *New PSR* | *Pt.-years observation* | *Incidence (per 100 pt.-years)* | *New PSR* | *Pt.-years observation* | *Incidence (per 100 pt.-years)* | *Incidence (per 100 pt.-years)* |
| 0–9 | 0 | 56 | 0·0 | 0 | 37 | 0·0 | 0·0 |
| 10–14 | 2 | 118 | 1·7 | 7 | 121 | 5·8 | 3·8 |
| 15–19 | 12 | 176 | 6·8 | 5 | 181 | 2·8 | 4·8 |
| 20–24 | 10 | 115 | 8·7 | 11 | 152 | 7·2 | 7·9 |
| 25–29 | 1 | 21 | 4·8 | 8 | 83 | 9·6 | 8·6 |
| 30–39 | 2 | 40 | 5·0 | 9 | 108 | 8·3 | 7·4 |
| 40 plus | 2 | 43 | 4·6 | 2 | 70 | 2·9 | 3·5 |
| Total | 29 | 569 | 5·1 | 42 | 752 | 5·6 | 5·4 |

The excess of females examined (58% SS, 54% SC) reflects the attendance pattern of the clinic. Proportionately more of the SC patients were examined because of the known higher prevalence of PSR in SC disease and because they comprised a greater proportion of the adult clinic.

## PREVALENCE

The prevalence of PSR at the initial eye examination by age group in SS and SC disease is shown in Tables I and II respectively. Proliferative retinopathy was more common in SC than SS disease ($p<0{\cdot}001$) and increased with age in both genotypes. In SS disease PSR was first observed in the 15–19 years age group, and the prevalence increased gradually to peak in patients aged 30 years and over. The apparent fall in frequency of PSR in male SS patients from the 30–39 year age group to the 40 years and over age group was not significant. In SC disease PSR was first seen in the 10–14-year age group, and the prevalence of PSR increased steeply with age, reaching maximum frequencies in SC males in the 25–29-year age group and in SC females aged 40 and above. As to the effect of sex, males with SC disease were significantly more likely to have PSR than females ($p<0{\cdot}001$), but a similar trend in SS disease was not significant ($p=0{\cdot}14$). Symptoms attributable to PSR prior to first eye examination occurred in 10% SC patients and 1% SS patients, but symptomatic referral did not significantly affect the prevalence data.

## INCIDENCE

The development of PSR for the first time was observed in 41 patients with SS disease (Table III) and in 71 patients with SC disease (Table IV). In SS disease incident cases were first observed in the 15–19 year age group, and the incidence rate appeared to increase to those aged 25 and over, though this trend was not significant. In SC disease incident cases first occurred in the 10–14 year age group, and incidence rates peaked at age 20–24 in males and at age 25–29 in females. However, neither the age related trend nor the apparent sex difference in SC disease reached statistical significance.

## BILATERALITY

The frequency of bilateral involvement was examined, since this may distinguish the role of systemic factors (favouring bilateral involvement) from local factors (favouring unilateral involvement). Bilateral PSR occurred in 44/90 (49%) of patients with SS disease and in 170/243 (70%) of patients with SC disease, being significantly more common ($p<0{\cdot}001$) in SC disease. In both genotypes bilateral PSR was more common than would be expected if PSR had developed independently in the second eye ($p<0{\cdot}001$).

The development of bilateral PSR was prospectively observed in the study in 59 patients (18 SS, 41 SC). The interval between onset in the first and second eye was examined, since simultaneous onset might reflect some acute haematological change or clinical event relevant to the pathogenesis of PSR. In only three patients (1 SS, 2 SC) was PSR observed to develop in both eyes within one year, and in none did this occur simultaneously. In 14 patients (2 SS, 12 SC) the interval between onset in the first and second eyes was at least one year. In the remaining 42 patients the intervals between visits were too irregular to provide useful data.

## FAMILIAL CLUSTERING

The clustering of PSR affected patients within families was examined, since this might identify other genetic factors relevant to the development of PSR. In SS disease there were insufficient numbers of PSR affected patients to conduct this

TABLE V *Familial clustering of proliferative sickle retinopathy within families with SC disease*

| | *Number of siblings examined* | | | | | |
|---|---|---|---|---|---|---|
| | *2* | | | *3* | | |
| *Sibling with PSR* | *Observed (O)* | *Expected (E)* | *O-E* | *Observed (O)* | *Expected (E)* | *O-E* |
| 0 | 11 | 10·1 | 0·9 | 3 | 2·3 | 0·7 |
| 1 | 13 | 15·1 | −2·1 | 4 | 4·5 | −0·5 |
| 2 | 10 | 8·8 | 1·2 | 2 | 3·7 | −1·7 |
| 3 | – | – | – | 3 | 1·5 | 1·5 |

analysis. In SC disease there were 62 families with two or more affected siblings for whom the results of eye examinations were available (34 sets of two siblings, 12 sets of three siblings, and one set of six siblings). From age/sex specific prevalence data the probability of observing 0, 1, 2, or 3 siblings with PSR within each family was calculated. Summing these probabilities over families gave the expected numbers of families with 0, 1, 2, or 3 cases of PSR. Familial clustering would be indicated by an excess of families in which none or all of the siblings had PSR, which was not supported by the data (Table V). In the family of six siblings five had PSR, but this was not an improbable occurrence (1-sided exact probability test, p=0·15).

### HAEMATOLOGICAL VARIABLES

Comparison of haematological variables in patients with and without PSR showed significant associations of PSR with high Hb in SS males and a low HbF in SS patients of both sexes (Table VI). In SC disease there were associations with high Hb and high MCHC in males and with high MCV and low HbF in both sexes (Table VII).

Further examination of these relationships by multiple logistic regression analysis, which allows for effects of age and for interrelationships between haematological variables, showed that in SS disease both the high Hb for males and low HbF in both sexes remained significant (Table VIII). In SC disease all the significant relationships in males apparent on simple regression were no longer significant, though a low HbF and a high MCV remained significant in females. The effects of these factors can be illustrated by using the fitted logistic regression models to predict the probability of PSR. For example, a 35-year-old SS male with Hb 7 g/dl and HbF 6% would have a 6% chance of having PSR, whereas with Hb 10 g/dl and HbF 1·5% this would rise to 53%. A 35-year-old SC female with Hb 12 g/dl, mean corpuscular haemoglobin concentration (MCHC) 35 g/dl, mean cell volume (MCV) 75 fl, and HbF 2% would have a 29% chance of having PSR, though changing the latter two indices to 90 fl and 0·5% would increase this chance to 92%.

The α globin gene number was known in 351/786 (45%) SS patients. PSR was observed at the first visit in 2/42 (5%) SS patients homozygous for α thalassaemia, 8/116 (7%) SS patients heterozygous for α thalassaemia, and 15/192 (8%) SS patients with a normal α globin gene complement, with no significant difference between groups. Among SS patients with a normal α globin gene complement PSR occurred in 10/82 (12%) males compared with 5/110 (5%) females, though this difference just failed to reach statistical significance (z=1·95, p=0·051). No α globin gene number data were available in SC disease.

## Discussion

The observation that proliferative sickle retinopathy occurs at such high frequency in a generally benign genotype of sickle cell disease is of considerable interest. Most patients with sickle cell haemoglobin C disease run a mild clinical

TABLE VI *Some haematological indices in 740 patients with SS disease with and without proliferative sickle retinopathy*

| | *Males* | | | | | *Females* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *PSR +ve (n=41)* | | *PSR −ve (n=265)* | | *Significance* | *PSR +ve (n=46)* | | *PSR −ve (n=388)* | | *Significance* |
| | *Mean* | *SD* | *Mean* | *SD* | *t* | *Mean* | *SD* | *Mean* | *SD* | *t* |
| Hb (g/dl) | 8·81 | 1·59 | 8·06 | 1·20 | 3·65*** | 7·75 | 1·16 | 7·88 | 1·05 | 0·76 |
| MCHC (g/dl) | 33·8 | 1·5 | 33·9 | 1·7 | 0·43 | 33·5 | 1·6 | 33·9 | 1·7 | 1·49 |
| MCV (fl) | 86·7 | 8·0 | 87·4 | 7·9 | 0·50 | 89·2 | 8·7 | 89·3 | 7·9 | 0·08 |
| Reticulocytes (%) | 9·5 | 3·4 | 10·5 | 3·6 | 1·71 | 10·5 | 3·5 | 10·1 | 3·3 | 0·73 |
| Log$_{10}$ (HbF+1)† | 0·58 (2·8) | 0·22 | 0·69 (3·9) | 0·25 | 2·63** | 0·71 (4·1) | 0·23 | 0·80 (5·3) | 0·24 | 2·71** |
| Platelets ($\times 10^9$/l) | 372 | 122 | 417 | 142 | 1·88 | 419 | 130 | 423 | 138 | 0·16 |
| Log$_{10}$ bilirubin† | 1·70 (50) | 0·21 | 1·68 (48) | 0·23 | 0·68 | 1·63 (43) | 0·22 | 1·65 (45) | 0·21 | 0·68 |
| Serum iron (mmol/l) | 16·8 | 4·9 | 15·9 | 4·7 | 1·55 | 15·0 | 4·3 | 16·3 | 5·5 | 1·50 |

†Figures in parentheses are means re-expressed in original units, HbF(%), bilirubin (mmol/l). Significance: *p<0·05; **p<0·01; ***p<0·001.

TABLE VII *Some haematological indices in 441 patients with SC disease with and without proliferative sickle retinopathy*

| | *Males* | | | | | *Females* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *PSR +ve (n=105)* | | *PSR −ve (n=97)* | | *Significance* | *PSR +ve (n=97)* | | *PSR −ve (n=142)* | | *Significance* |
| | *Mean* | *SD* | *Mean* | *SD* | *t* | *Mean* | *SD* | *Mean* | *SD* | *t* |
| Hb (g/dl) | 12·82 | 1·36 | 12·14 | 1·35 | 3·52*** | 11·23 | 1·17 | 11·30 | 1·03 | 0·50 |
| MCHC (g/dl) | 35·9 | 1·2 | 35·5 | 1·4 | 2·31* | 35·5 | 1·2 | 35·7 | 1·4 | 0·87 |
| MCV (fl) | 84·9 | 6·2 | 80·6 | 7·0 | 4·64*** | 83·3 | 6·0 | 80·4 | 6·6 | 3·42*** |
| Reticulocytes (%) | 4·0 | 1·4 | 3·9 | 1·5 | 0·59 | 3·8 | 1·3 | 4·0 | 1·7 | 0·74 |
| Log$_{10}$ (HbF+1)† | 0·26 (0·8) | 0·15 | 0·32 (1·1) | 0·21 | 2·42* | 0·28 (0·9) | 0·15 | 0·36 (1·3) | 0·20 | 3·13*** |
| Platelets ($\times 10^9$/l) | 265 | 114 | 287 | 108 | 1·32 | 263 | 106 | 264 | 99 | 0·10 |
| Log$_{10}$ bilirubin† | 1·40 (25) | 0·20 | 1·38 (24) | 0·20 | 0·51 | 1·31 (20) | 0·16 | 1·31 (20) | 0·22 | 0·26 |
| Serum iron (mmol/l) | 15·3 | 5·1 | 15·5 | 4·5 | 0·41 | 14·4 | 4·5 | 14·0 | 4·4 | 0·70 |

†Figures in parentheses are means in original units, HbF(%), bilirubin (mmol/l). Significance: *p<0·05; **p<0·01; ***p<0·001.

TABLE VIII *Relationship of selected haematological indices and proliferative sickle retinopathy analysed by multiple logistic regression*

| | *SS* | | | | *SC* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Males* | | *Females* | | *Males* | | *Females* | |
| | *Slope* | *p* | *Slope* | *p* | *Slope* | *p* | *Slope* | *p* |
| Hb | 0·56 | <0·001 | 0·26 | 0·1 | −0·01 | 0·99 | −0·10 | 0·6 |
| $Log_{10}$ (HbF+1) | −2·55 | 0·003 | −2·53 | <0·001 | −1·12 | 0·3 | −4·5 | <0·001 |
| MCV | | | | | 0·05 | 0·08 | 0·13 | <0·001 |
| MCHC | | | | | 0·21 | 0·2 | −0·30 | 0·07 |

course with near normal haematology and infrequent vaso-occlusive episodes. Patients with homozygous sickle cell disease generally have frequent vaso-occlusion and a severe clinical course, yet proliferative sickle retinopathy is significantly less frequent. This enigma suggests that the two genotypes may be useful models for understanding the risk factors for PSR.

One hypothesis attempting to reconcile this unexpected observation envisaged three models with different vaso-occlusive tendencies.[10 11] Patients with low vaso-occlusive indices would be unlikely to develop retinal ischaemia and therefore have no stimulus to develop PSR. Patients with moderate vaso-occlusive indices would develop peripheral retinal closure and proceed to the development of preproliferative or proliferative disease. Patients with high vaso-occlusive indices would develop extensive peripheral retinal vascular closure, with a stimulus to PSR formation, but would proceed to occlude preproliferative arteriovenous anastomoses or nascent PSR. It was proposed that SC disease represented the intermediate model, with sufficient vaso-occlusion to produce retinal ischaemia but insufficient to occlude the lesions of developing PSR. An analogous situation would be the persistence of splenomegaly in SS patients with high levels of HbF,[12] representing the survival of a capillary bed not damaged by vaso-occlusion and hence an expression of pathological mildness.

This hypothesis implies that the risk factors for retinal vaso-occlusion may differ from those for PSR. Only limited data are available on the risk factors for peripheral retinal vaso-occlusion. Observations in the Jamaican cohort study confirmed that closure generally increased progressively with age, was more common in males than females at an early age, and was not significantly more frequent in SS disease.[13] Analysis of haematological risk factors in SS disease showed that retinal closure was significantly associated with low total haemoglobin, low fetal haemoglobin, a high reticulocyte count, and high counts of irreversibly sickled cells.[14] The effect of total haemoglobin disappeared on multiple logistic regression,[14] suggesting that its effect was entirely secondary to its relationship with HbF, but a later matched pairs analysis of patients with minimal or complete closure[13] showed an independent effect of haemoglobin level. In SS disease, therefore, closure was associated with low Hb, low HbF, high reticulocyte, and high ISC counts whereas PSR was associated with a high Hb (males only) and low HbF. In SC disease closure was associated with a high reticulocyte count,[14] though this was not apparent on a later matched pairs analysis, which showed effects of high MCV and low platelet counts.[13] By contrast haematological risk factors for PSR in SC disease were apparent only in females and included a high MCV and low HbF.

The results of analysis for haematological risk factors for PSR in the present study are broadly similar to previous observations. In SS disease observations in males were identical to those of Hayes *et al*,[1] whereas in females a previously noted and unexplained contribution of low serum iron was lost, and an effect of low HbF has emerged in the present study. In SC disease the results on simple regression in males were again identical to those of an earlier study,[2] though logistic regression in the currently available larger data set shows that none of the apparent contributions of high Hb, low HbF, high MCHC, and high MCV remain significant. In females only a low HbF was significant in the earlier study, but a high MCV also appears to be a risk factor.

These haematological data may contribute to the understanding of the mechanisms of PSR formation, since different indices are believed to affect flow in different sized vessels. Thus flow in large vessels is affected predominantly by viscosity (haemoglobin, haematocrit) or number of particles (red cell count), whereas flow in the capillary bed is affected by the characteristics of the individual red cells such as membrane deformability and intracellular viscosity. In sickle cell disease the latter is particularly affected not only by the MCHC but also by HbF, which affects the intracellular polymerisation of HbS. The haematological data are therefore more consistent with a capillary site of obstruction. Furthermore the lack of demonstrable differences in blood viscosity between groups with and without PSR in SS[11] and SC[10] disease is less consistent with a role of larger vessel flow. The elegant angiographic studies of Galinos *et al*[15] showing non-perfusion at or near Y shaped branches of the precapillary arterioles would be consistent with either interpretation.

Other observations in the present study have contributed to the understanding of PSR. Both the prevalence and incidence data show that PSR is rare in the first decade, suggesting that extensive retinal damage must have accumulated before the PSR develops. The high frequency of bilaterality suggest that systemic factors contribute to the development of PSR, though the lack of simultaneous development argues against a role of acute haematological change or a severe clinical event. The analysis of familial clustering was limited by the relatively small numbers available, and, though showing a trend in that there was a slight excess of families in which all or none of the siblings had PSR, the differences were far short of significance, contrary to our clinical impression.

Do the available data fit the hypothesis? The first model of low vaso-occlusive indices is self-evident, since PSR does not develop in the absence of retinal ischaemia. However, this is likely to be a small group, since retinal closure occurred in approximately 90% children by 12 years of age,[13] the factors protecting against closure being either homozygous α thalassaemia or very high levels of HbF. The middle group with moderate vaso-occlusive indices should include the majority of SC patients and a smaller proportion of those with SS disease. The group with high vaso-occlusive indices should contain predominantly patients with SS disease. This genotype is already recognised to be associated with increased autoinfarction of established PSR,[16] but, if the hypothesis is correct, patients with the greatest vaso-occlusion should be experiencing preproliferative changes and not proceeding to the development of PSR.

Testing the hypothesis requires an accurate indicator of vaso-occlusive tendency. Using HbF level as such an indicator, we could not demonstrate a lower frequency of PSR among those with the lowest HbF levels. Although inconsistent with the hypothesis, this observation casts doubt on the validity of HbF as an indicator of vaso-occlusion and does not necessarily refute the hypothesis.

We thank other ophthalmologists associated with the Jamaican ophthalmic studies, especially Mr Patrick Condon, Robert Acheson, and Brendan Moriarty, who have all contributed to the data. We thank Dr Douglas Higgs for the studies on α globin gene number.

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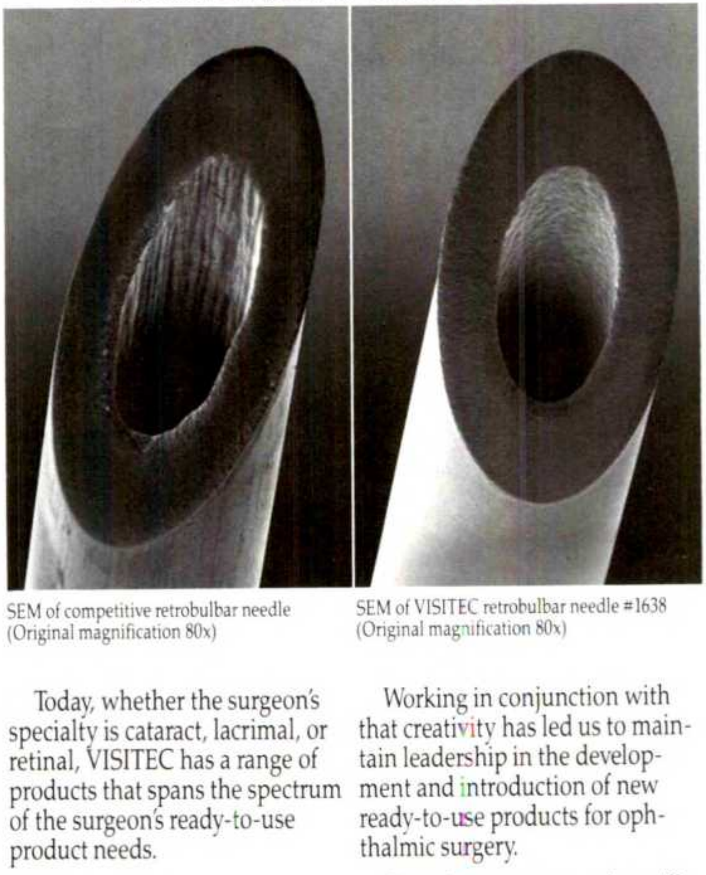

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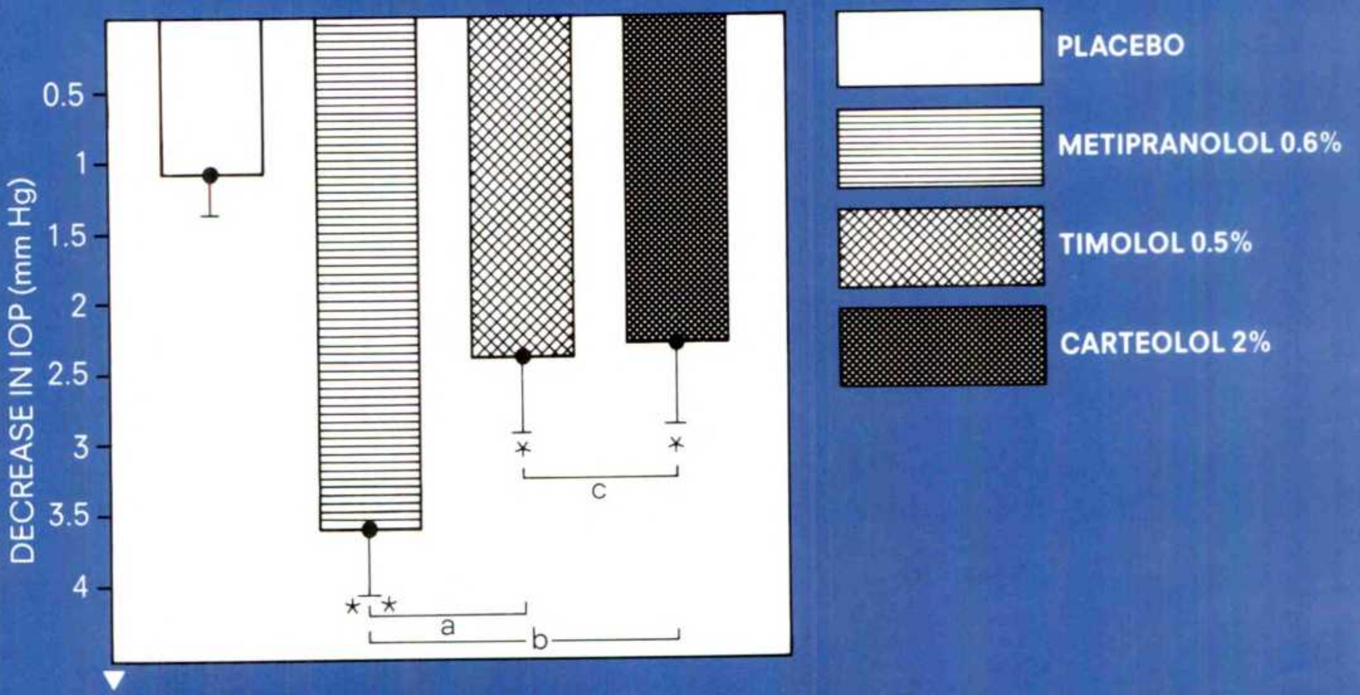

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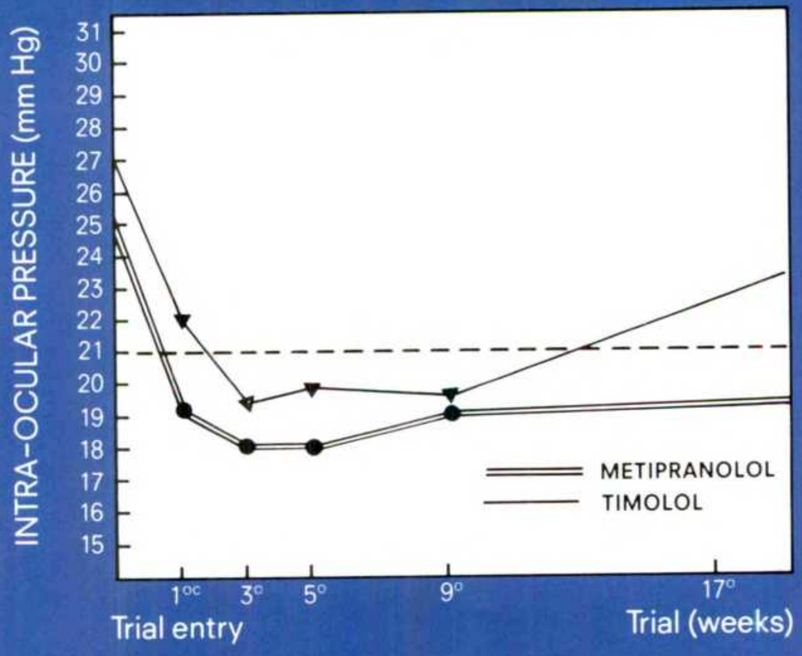

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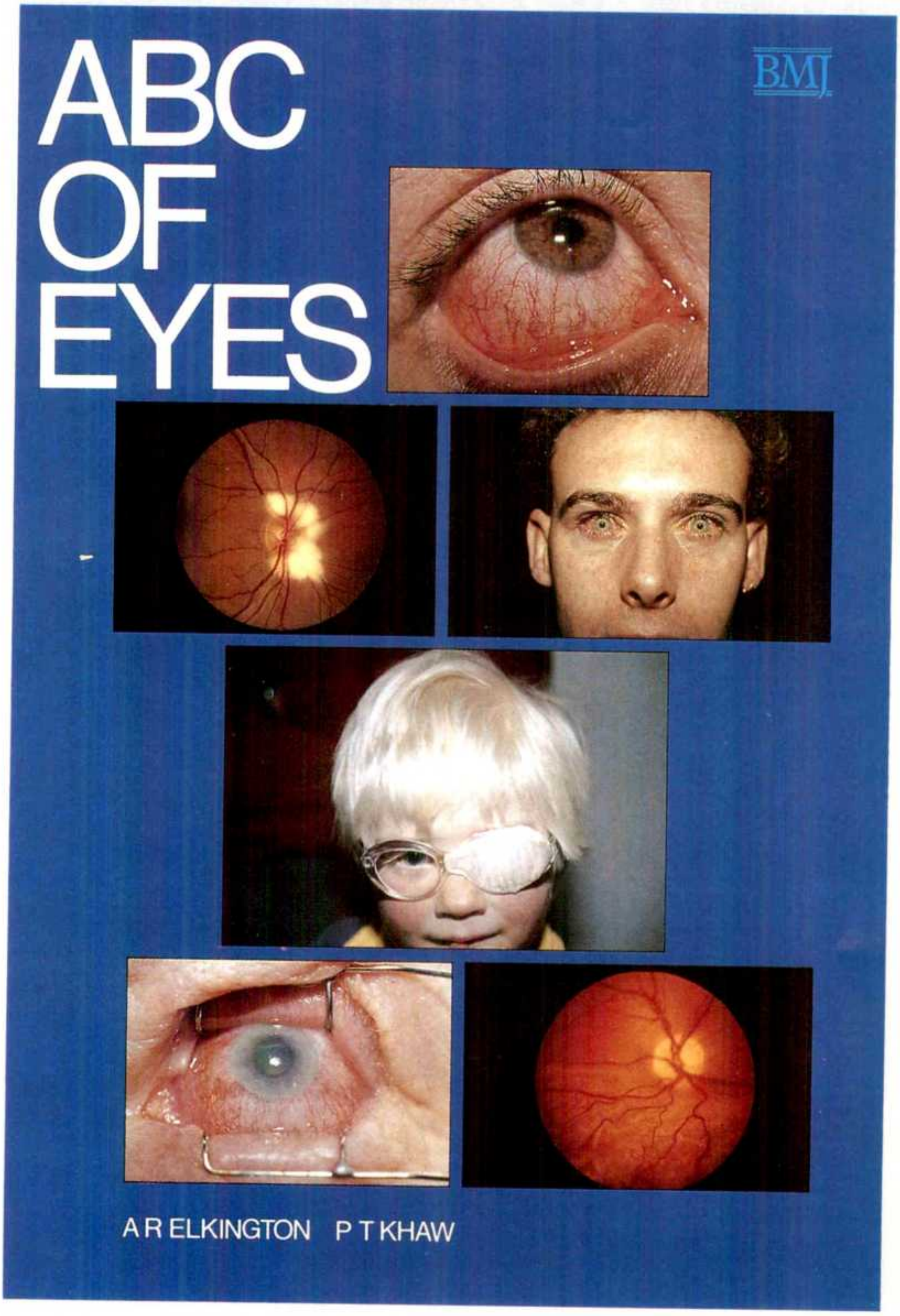

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# Retinal laser lenses: magnification, spot size, and field of view

Martin A Mainster, Janet L Crossman, Phillip J Erickson, Gregory L Heacock

**Abstract**

**Proper use of ophthalmoscopic contact lenses for retinal photocoagulation requires knowledge of their comparative magnification, spot size, and field of view. We determined these parameters for four commonly used lenses, using data measured from optical components of the lenses and a commonly used photocoagulator slit-lamp and spot size changer. A Krieger lens has 8% more working field of view and 29% less magnification than a Goldmann lens. A Panfundoscope lens has 84% more working field of view and 24% less magnification than a Goldmann lens. A Mainster lens has 58% more working field of view and 3% more magnification than a Goldmann lens. For Goldmann, Krieger, Panfundoscope, and Mainster lenses, respectively, retinal spot size is 8%, 53%, 41%, and 5% greater than photocoagulator spot size settings. The field of view of each lens is increased in myopic and decreased in hyperopic patients. Anterior segment irradiance is higher than retinal irradiance for 1000 μm spot size settings with a Panfundoscope or Mainster lens, and this setting should be avoided, especially in patients with hazy ocular media.**

Retinal temperature increase from laser photocoagulation is proportional to retinal irradiance, the laser power per unit area reaching the retinal surface.[1 2] Decreasing laser spot size increases retinal irradiance and tissue effects for a particular combination of power and exposure duration settings. Thus, knowledge of laser spot size is important for ensuring safety and reproducibility of clinical results from retinal photocoagulation.

Laser photocoagulators have calibrated spot size selectors, but the actual retinal spot size they produce depends on the particular contact lens used for laser beam delivery and the patient's refractive error. New contact lenses have been introduced in recent years to facilitate ophthalmoscopy during retinal photocoagulation.[3-9] Each lens has its own advantages, but optimal lens usage requires knowledge of comparative lens magnification, spot size, and field of view. These data were determined from computerised ray tracing models of the human eye, four commonly used ophthalmoscopic lenses, and a standard slit-lamp and photocoagulator spot size changer.

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## Materials and methods

Goldmann, Krieger, Panfundoscope, and Mainster ophthalmoscopic contact lenses were studied. Table I summarises their characteristics. Optical parameters of a Zeiss 30 SL-M slit-lamp (Carl Zeiss, Oberkochen, West Germany) were used for field of view calculations, and those of a Coherent Model 920 photocoagulator spot size changer (Coherent Medical Division, Palo Alto, CA) were used for spot size calculations. The spot size changer is parfocal for 50 and 100 μm spot sizes, and defocuses for larger spot sizes.

The radius of curvature and back focal length were measured for each ophthalmoscopic lens, slit-lamp, and spot-size changer component with a Zygo Mark I interferometer (Zygo, Middlefield, CT). Centre thicknesses, apertures, and lens separations were measured directly. A modified Le Grand-El Hage unaccommodated theoretical model eye[10] was used in all calculations, with an anterior corneal radius of 7·824 mm, and a conic constant of −0·870852 to correct for axial spherical aberrations[11] of the human eye. Calculations were performed with the Super-Oslo optical design program (Sinclair Optics, Inc, Fairport, NY).

## Results

Goldmann and Krieger lenses produce erect, virtual ophthalmoscopic images, while Panfundoscope and Mainster lenses have inverted, real images. The orientation, axial location, and magnification of the ophthalmoscopic image of each lens is illustrated in Figures 1–4.

Magnification and field of view are critical parameters for determining which lens is best for a particular clinical problem. Table II presents computed magnification and field of view for the four lenses. The lateral magnification was determined for each lens from ray tracing studies with ophthalmoscopic lens and model eye parameters. Positive and negative lateral magnification connote erect and inverted image orientation respectively. Relative magnification is the absolute value of lateral magnification divided by the lateral magnification of a Goldmann lens. It indicates that Goldmann and Mainster lenses have similar magnification, but that Panfundoscope and Kreiger lens magnification is much smaller. Axial magnification is the square of lateral magnification.

Field of view computations were performed for each slit-lamp, ophthalmoscopic lens, and model eye system. These calculations were carried out relative to the nodal point of the eye model on the assumption of a 7 mm dilated pupil diameter. Instantaneous field of view is the maximum field observable at one time without tilting the lens. Working field of view is the

TABLE I *Ophthalmoscopic laser contact lenses*

| *Parameter* | *Goldmann** | *Krieger†* | *Panfundoscope‡* | *Mainster†* |
|---|---|---|---|---|
| Anterior surface | Flat | Concave, spherical | Convex, spherical | Convex, aspherical |
| Power§ | −67 | −92 | +85 | +61 |
| Image type | Virtual, erect | Virtual, erect | Real, inverted | Real, inverted |
| Image location | Posterior capsule | Vitreous humour | Biconvex lens | Air |

*Haag-Streit, Bern, Switzerland. †Ocular Instruments, Bellevue, WA, USA. ‡Rodenstock, Munich, West Germany. §Refractive power in dioptres of the entire ophthalmoscopic lens system in air, as determined from direct measurement.

maximum field obtainable with a 15° tilt to either side of the optical axis. For each lens the field stop (which limits the field of view[12,13]) was the patient's iris for pupil diameters up to 7 mm. The aperture stop (which limits the amount of light reaching the image[12,13]) is located in the slit-lamp's telescopic section.

Table II shows that the inverted image lenses have a considerably greater field of view than the erect image lenses. Table III presents the results of similar magnification and field of view calculations carried out for ±3 dioptre axial ametropia. Results are presented as percentage differences from emmetropic eye findings, with positive and negative percentages indicating higher or lower values respectively. Ametropia has little effect on the magnification of the erect image ophthalmoscopic lenses, but the magnification of inverted image lenses is decreased in myopia and increased in hyperopia. Field of view is increased in myopia and decreased in hyperopia for each of the lenses.

Spot size calculations were performed for optical systems consisting of the spot size charger, an ophthalmoscopic lens, and the model eye. Table IV presents spot size changer settings and the spot sizes they produce at the posterior surfaces of the cornea, crystalline lens, and neural retina. It shows that spot size settings are reasonably accurate for Goldmann and Mainster lenses, but that retinal spot size is greater than the setting by approximately 40% and 50% for the Panfundoscope and Kreiger lenses, respectively. Table IV also shows that, for 1000 μm settings, corneal spot size is 60% and 23% smaller than retinal spot size for the Panfundoscope and Mainster lenses respectively. Thus, for a 1000 μm setting, corneal irradiance may be up to 6·2 or 1·7 times greater than retinal irradiance for a Panfundoscope or Mainster lens, respectively.

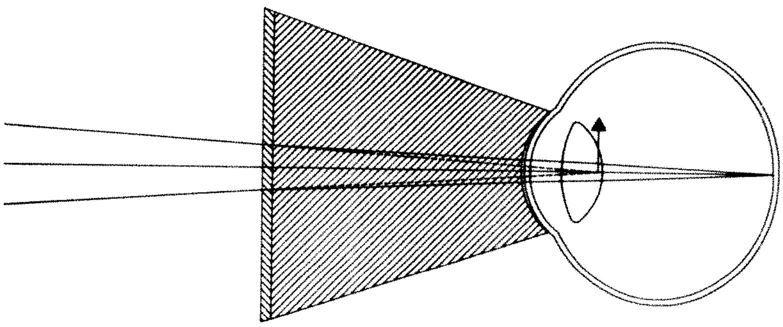

*Figure 1: The Goldmann lens has a flat anterior surface and produces an erect, virtual ophthalmoscopic image located near the posterior surface of the crystalline lens.*

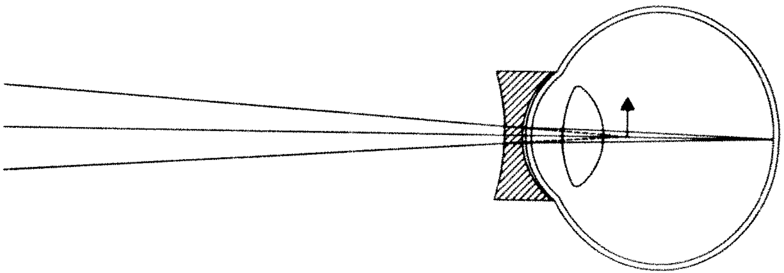

*Figure 2: The Krieger lens has a concave anterior surface and produces an erect, virtual ophthalmoscopic image located in the anterior vitreous humour.*

## Discussion

The three-mirror Goldmann lens has been a standard ophthalmoscopic lens since biomicroscopic laser photocoagulation began, providing excellent posterior pole magnification as well as peripheral retinal observation through internal reflecting surfaces. The chief disadvantage of the Goldmann lens, its limited field of view, prompted development of the three other ophthalmoscopic lenses discussed in this paper. Each lens is a different choice in balancing field of view with ophthalmoscopic image magnification.

The concave surfaced Krieger lens was developed in 1966, and various modifications have been introduced subsequently.[8,9] The Krieger lens provides an erect, virtual image as does the Goldmann lens, but its ophthalmoscopic image is displaced posteriorly from the posterior capsule into the anterior vitreous (see Figs 1 and 2). As shown in Table II, the Krieger lens has an 8% greater working field of view than the Goldmann lens, but this is accomplished at a substantial 29% decrease in lateral magnification.

Introduction of the Panfundoscope lens in 1969 increased the ease and safety of panretinal photocoagulation.[4-6] The Panfundoscope lens produces an inverted, real image located in its spherical biconvex anterior lens element, as shown in Figure 3.

The Panfundoscope lens has a working field of view 84% greater than that of the Goldmann lens, accomplished at a 24% reduction in lateral magnification. This reduced magnification is not

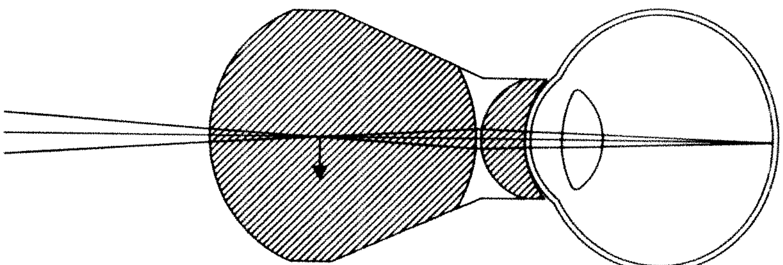

*Figure 3: The Panfundoscope lens has a biconvex, spherical anterior lens element and produces an inverted, real image inside the biconvex lens.*

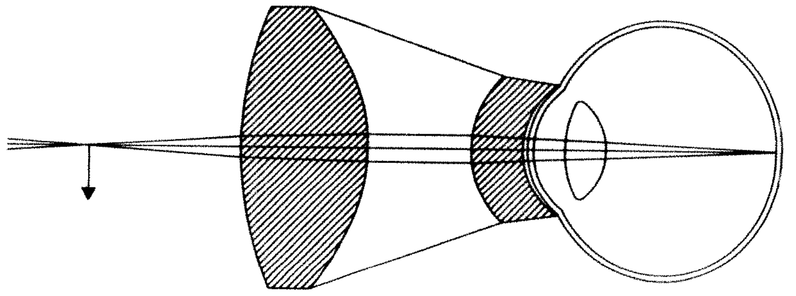

*Figure 4: The Mainster lens has a biconvex, aspherical anterior lens element and produces an inverted, real image anterior to the biconvex lens.*

TABLE II *Magnification and field of view for laser ophthalmoscopic contact lenses*

| *Parameter* | *Goldmann* | *Krieger* | *Panfundoscope* | *Mainster* |
|---|---|---|---|---|
| Lateral magnification | +0·93 | +0·66 | −0·71 | −0·96 |
| Relative magnification | 1·00 | 0·71 | 0·76 | 1·03 |
| Axial magnification | 0·86 | 0·43 | 0·51 | 0·92 |
| Instantaneous field of view* | ±18° | ±21° | ±60° | ±45° |
| Working field of view (with 15° tilt)* | ±38° | ±41° | ±70° | ±60° |

*Half-field angle.

TABLE III *Change in magnification and working field of view in patients with axial myopia and hyperopia*

| *Parameter* | *Goldmann* | *Krieger* | *Panfundoscope* | *Mainster* |
|---|---|---|---|---|
| Magnification (myope, −3 D) | 0 | −1·5% | −4·2% | −5·2% |
| Magnification (hyperope, +3 D) | 0 | 0 | +5·6% | +4·2% |
| Field of view (myope, −3 D) | +5·3% | +4·9% | +8·6% | +6·7% |
| Field of view (hyperope, +3 D) | −5·3% | −2·4% | −5·7% | −6·7% |

a disadvantage in panretinal photocoagulation, but it limits the usefulness of the Panfundoscope lens in procedures requiring high lateral and axial magnification, such as photocoagulation for choroidal neovascularisation. Increasing biomicroscopic magnification cannot compensate for reduced ophthalmoscopic image magnification, because it cannot increase the resolution of the ophthalmoscopic image.

The Mainster lens was introduced in 1986, providing higher magnification but a smaller field of view than the Panfundoscope lens. As shown in Figure 4, the Mainster lens produces an inverted, real image located in front of its biconvex aspheric anterior lens element. Laser beam distortion at the edge of the field of view is minimised by the aspheric element. Since the ophthalmoscopic image is anteriorly displaced, however, using the Mainster lens with older slit-lamps of reduced anteroposterior travel (for example, Zeiss model 125) may require moving a hyperopic or exophthalmic patient's forehead several millimetres backwards from the headrest.

The Mainster lens has a working field of view 58% greater than that of a Goldmann lens, and its lateral and axial magnification are greater than those of the Goldmann lens by 3% and 7% respectively. But the working field of view of a Mainster lens is 14% less than that of the Panfundoscope lens, so the peripheral retinal area it spans is 21% less than that of a Panfundoscope lens. Since the Mainster lens has both high magnification and a wide field of view, it is useful for detecting retinal thickening, following angiographic landmarks to retinal targets, and performing focal as well as panretinal photocoagulation.

TABLE IV *Laser beam diameter at the cornea, lens, and retina versus photocoagulator spot size setting, for the laser beam focused on the retina**

| *Tissue (posterior surface)* | *Spot size setting* (μm) | *Tissue spot size* (μm) | | | |
|---|---|---|---|---|---|
| | | *Goldmann* | *Krieger* | *Panfundoscope* | *Mainster* |
| Cornea | 100 | 1335 | 979 | 959 | 1285 |
| | 200 | 1321 | 1004 | 866 | 1164 |
| | 500 | 1432 | 1187 | 703 | 960 |
| | 1000 | 1793 | 1616 | 567 | 804 |
| Lens | 100 | 1048 | 791 | 760 | 1000 |
| | 200 | 1071 | 857 | 733 | 941 |
| | 500 | 1256 | 1138 | 742 | 887 |
| | 1000 | 1697 | 1700 | 859 | 934 |
| Retina | 100 | 108 | 153 | 141 | 105 |
| | 200 | 216 | 306 | 282 | 210 |
| | 500 | 541 | 764 | 704 | 524 |
| | 1000 | 1081 | 1529 | 1409 | 1048 |

*For example, with the laser beam focused on the retina and a 1000 μm photocoagulator spot size setting, beam diameter with a Panfundoscope lens will be 567 μm, 859 μm, and 1409 μm at the posterior surfaces of the cornea, lens, and retina respectively.

The Panfundoscope and Mainster lenses share a common disadvantage.[9,14] As noted above, anterior segment irradiance may exceed retinal irradiance for a 1000 μm spot size setting, increasing the risk of cornea or lens damage if ocular media are hazy.[9,14] In this situation spot size settings should be restricted to 500 μm or less. Both lenses also share a slight sensitivity to ametropia, as shown in Table III. Changes in magnification are probably not clinically significant, but for a +3 dioptre hyperopic patient the viewable peripheral retinal area is decreased by 18% and 21% for Panfundoscope and Mainster lenses respectively.

The accuracy of the preceding calculations is limited by that of the standard eye model we employed. Within that constraint, Tables I–IV offer a self-consistent comparison of contemporary ophthalmoscopic contact lens performance.

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# Bilaterality of drusen

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## Abstract

**The characteristics of drusen in 81 patients with bilateral drusen as a manifestation of age related disease were analysed for symmetry between the two eyes. It was found that there was close concordance with respect to drusen size, number, density, and fluorescence which was greater than would have been expected by chance alone. This finding implies that drusen may result from metabolic malfunction specific to the patient rather than the non-specific result of aging.**

Loss of central vision in age related macular disease is due to lesions which occur in response to deposition of abnormal material in Bruch's membrane.[1] This abnormal material is believed to be derived from the retinal pigment epithelium.[2-6]

There is good evidence that the retinal pigment epithelial cells discharge cytoplasmic material throughout life into the inner portion of Bruch's membrane by apoptosis.[7-10] By this mechanism it is conceived that the pigment epithelium voids the products of phagosomal degradation and other metabolic activities. It is thought that the discharged material subsequently diffuses through Bruch's membrane and is cleared by the choroidal capillaries. The accumulation of debris in Bruch's membrane results from failure to clear the cytoplasmic contents deposited into this region. This may be due to changes in the fibres or inter-fibre matrix of Bruch's membrane whereby outward diffusion of material towards the choriocapillaris is hampered. In the dog it has been shown that Bruch's membrane impedes diffusion of only the largest molecules,[11] though decreased hydraulic conductivity occurs in man with age.[12] Alternatively it is possible that the material discharged into Bruch's membrane is abnormal, and in particular may contain large molecules and membrane complexes, such that free outward diffusion does not occur. Change in the nature of the material discharged into Bruch's membrane may reflect altered metabolism of the pigment epithelium, and in particular failure of the degradative lysosomal enzyme systems.

Discrete abnormal deposits in the inner portion of Bruch's membrane, when large, can be detected clinically as drusen.[13] Their appearance and distribution may vary widely from one patient to another, and histological studies imply that the composition of the deposits differs from one eye to another.[14 15] However, changes are rarely unilateral, and some symmetry exists between the right and left eyes for the number and type of drusen in the macula area.[16-20] In most of these studies limited data were obtained, and the aim of this project was to verify these observations. Drusen characteristics were analysed in order to examine whether or not symmetry of drusen exists between the two eyes of a patient which is greater than might have been expected by chance alone. If symmetry were proved, it would imply that drusen may result from metabolic changes specific to the patient rather than being non-specific results of aging.

## Patients and methods

A retrospective study was undertaken of the clinical records, colour photographs, and fluorescein angiograms of a continuous series of 81 patients who were seen in 1983 and 1984 with the following attributes: all were over 50 years of age, they had minimal or no visual symptoms and good visual acuity, and had drusen at each macula but no signs of geographic atrophy, pigment epithelium detachment, or choroidal neovascularisation.

Photographs and angiograms of each patient were analysed by two authors independently for number, size, density, and early and late angiographic behaviour of the drusen by means of a grading scheme which has been described.[21 22] The posterior pole was divided into two areas: within (central) and outside (peripheral) 1600 μm of the foveola. The drusen in these areas were analysed according to their number (fewer than 10, 10 to 20, more than 20), their size (less than 50 μm, 50 to 500 μm, greater than 500 μm), and the distribution was classified as scattered, subconfluent, or confluent. Fluorescence of drusen was assessed as equal to choroidal fluorescence, slightly brighter than choroidal fluorescence, or brightly fluorescent during the dye transit and 3 minutes after dye entry. In most cases the drusen were uniform in size, distribution, and fluorescence in each area; when this was not the case the classification was determined by the largest, most densely

TABLE IA *Drusen number: central*

| | *Right eye* | | | | |
|---|---|---|---|---|---|
| | *Number* | *<10* | *10–20* | *>20* | *Total* |
| *Left eye* | 0 | 5 | 0 | 0 | 5 |
| | 10–20 | 1 | 5 | 2 | 8 |
| | <20 | 0 | 1 | 67 | 68 |
| | Total | 6 | 6 | 69 | 81 |

$\kappa=0{\cdot}82$; standard error=0·08.

TABLE IB *Drusen number: peripheral*

| | *Right eye* | | | | | |
|---|---|---|---|---|---|---|
| | *Number* | *0* | *<10* | *10–20* | *>20* | *Total* |
| *Left eye* | 0 | 10 | 0 | 0 | 0 | 10 |
| | <10 | 1 | 11 | 4 | 1 | 17 |
| | 10–20 | 0 | 3 | 7 | 3 | 13 |
| | >20 | 0 | 0 | 0 | 41 | 41 |
| | Total | 11 | 14 | 11 | 45 | 81 |

$\kappa=0{\cdot}77$; standard error=0·07.

TABLE IIA *Drusen size: central*

| | *Right eye* | | | | |
|---|---|---|---|---|---|
| | *Size* | *1* | *2* | *3* | *Total* |
| *Left eye* | 1 | 8 | 2 | 0 | 10 |
| | 2 | 1 | 55 | 5 | 61 |
| | 3 | 0 | 0 | 10 | 10 |
| | Total | 9 | 57 | 15 | 81 |

$\kappa$=0·77; standard error=0·07

TABLE IIB *Drusen size: peripheral*

| | *Right eye* | | | | | |
|---|---|---|---|---|---|---|
| | *Size** | *0* | *1* | *2* | *3* | *Total* |
| *Left eye* | 0 | 10 | 0 | 0 | 0 | 10 |
| | 1 | 0 | 14 | 4 | 0 | 18 |
| | 2 | 1 | 7 | 44 | 1 | 53 |
| | 3 | 0 | 0 | 0 | 0 | 0 |
| | Total | 11 | 21 | 48 | 1 | 81 |

$\kappa$=0·70; standard error=0·08

*0=no drusen. 1=<50μm. 2=50–500 μm. 3=>500 μm.

TABLE IVA *Drusen early fluorescence: central*

| | *Right eye* | | | | |
|---|---|---|---|---|---|
| | *Grade* | *1* | *2* | *3* | *Total* |
| *Left eye* | 1 | 2 | 0 | 0 | 2 |
| | 2 | 1 | 4 | 0 | 5 |
| | 3 | 0 | 0 | 7 | 7 |
| | Total | 3 | 4 | 7 | 14 |

$\kappa$=0·89; standard error=0·18

TABLE IVB *Drusen early fluorescence: peripheral*

| | *Right eye* | | | | | |
|---|---|---|---|---|---|---|
| | *Grade** | *0* | *1* | *2* | *3* | *Total* |
| *Left eye* | 0 | 1 | 0 | 0 | 0 | 1 |
| | 1 | 0 | 1 | 0 | 0 | 1 |
| | 2 | 0 | 1 | 4 | 0 | 5 |
| | 3 | 0 | 0 | 0 | 7 | 7 |
| | Total | 1 | 2 | 4 | 7 | 14 |

$\kappa$=0·89; standard error=0·18

*0=no drusen. 1=equal to choroidal fluorescence. 2=slightly brighter than choroidal fluorescence. 3=brightly fluorescent.

packed, and most fluorescent lesions. If the two readers disagreed, a third observer was asked to arbitrate, and the results were assigned after discussion.

The clinical data and the results of the drusen analysis were recorded and subjected to statistical analysis. The reliability of the assessment was examined by recording the percentage agreement between the two independent observers. Kappa statistics were used to assess the symmetry between the right and the left eye. These statistics evaluate the observed concordance beyond chance, related to the maximum possible agreement in excess of chance.[23] In most situations a $\kappa$ value of 0·8 indicate almost perfect concordance, and $\kappa$ values of 0·61–0·80 suggest substantial symmetry.[24]

## Results

Of the 81 patients 48 were females and 33 males. The average age of presentation was 61·3 years, range 50 to 81 years.

The interobserver reliability was 92·7% for the number, 93·9% for size, 89·6% for density, and 96·2% and 97·6% for early and late fluorescence of drusen.

Despite the presence of clustering, there was manifest symmetry between the two eyes for drusen size, density, and number which was greater than would have been expected by chance alone (Tables I–III).

Because early pictures of fluorescein angiograms in both eyes were not available for most patients, the analysis of symmetry for this characteristic is based only on the data from 14 patients. Despite this, symmetry was demonstrated between the two eyes in the central and peripheral areas of the macula (Table IV). For the analysis of the late fluorescein angiograms of both eyes 52 patients were available. The concordance between the right eye and the left was excellent in the central and peripheral parts of the macula (Table V).

## Discussion

For all analysed drusen characteristics the interobserver reliability was between 80% and 95%, which is comparable with the findings in other studies[25] and is considered to be an acceptable degree of agreement to justify conclusions.[26]

The results of our analysis recorded a good or excellent symmetry for all ophthalmoscopic and fluorescein angiographic characteristics of drusen in the central and peripheral areas of the

TABLE IIIA *Drusen density: central*

| | *Right eye* | | | | |
|---|---|---|---|---|---|
| | *Grades* | *1* | *2* | *3* | *Total* |
| *Left eye* | 1 | 8 | 1 | 0 | 9 |
| | 2 | 1 | 42 | 7 | 34 |
| | 3 | 0 | 4 | 18 | 22 |
| | Total | 9 | 47 | 25 | 81 |

$\kappa$=0·71; standard error=0·09

TABLE IIIB *Drusen density: peripheral*

| | *Right eye* | | | | | |
|---|---|---|---|---|---|---|
| | *Grade** | *0* | *1* | *2* | *3* | *Total* |
| *Left eye* | 0 | 10 | 0 | 0 | 0 | 10 |
| | 1 | 0 | 30 | 4 | 0 | 34 |
| | 2 | 1 | 3 | 29 | 0 | 33 |
| | 3 | 0 | 0 | 2 | 2 | 4 |
| | Total | 11 | 33 | 35 | 2 | 81 |

$\kappa$=0·81; standard error=0·08

*0=no drusen. 1=scattered. 2=subconfluent. 3=confluent.

TABLE VA *Drusen late fluorescence: central*

| | *Right eye* | | | | |
|---|---|---|---|---|---|
| | *Grade* | *1* | *2* | *3* | *Total* |
| *Left eye* | 1 | 2 | 0 | 0 | 2 |
| | 2 | 0 | 17 | 1 | 18 |
| | 3 | 0 | 0 | 32 | 32 |
| | Total | 2 | 17 | 33 | 52 |

$\kappa$=0·89; standard error=0·18

TABLE VB *Drusen late fluorescence: peripheral*

| | *Right eye* | | | | | |
|---|---|---|---|---|---|---|
| | *Grade** | *0* | *1* | *2* | *3* | *Total* |
| *Left eye* | 0 | 5 | 0 | 0 | 0 | 5 |
| | 1 | 0 | 1 | 0 | 0 | 1 |
| | 2 | 0 | 0 | 10 | 2 | 12 |
| | 3 | 0 | 0 | 0 | 34 | 34 |
| | Total | 5 | 1 | 10 | 36 | 52 |

$\kappa$=0·95; standard error=0·10

*0=no drusen. 1=equal to choroidal fluorescence. 2=slightly brighter than choroidal fluorescence. 3=brightly fluorescent.

posterior pole between both eyes in each patient. These observations are in accord with previous observations of bilateral incidence[17,19,20] as well as ophthalmoscopic assessment of symmetry.[16,18,20] Most striking was the symmetry of fluorescence between the two eyes, an attribute not investigated previously.

These findings have relevance to the concepts concerning drusen formation with age. The symmetry between the two eyes, despite the wide variation from one patient to another, implies that there is a degree of specificity in the determinants of disease. It is evident that the structural or metabolic characteristics which result in drusen formation have regional as well as quantitative variation peculiar to the individual. There is evidence that the degree of fluorescence of drusen gives some indication of their chemical composition.[14] If this is the case, the angiographic characteristics also imply that the chemical composition of drusen is patient specific. That there may be specific determinants of drusen formation would be in contrast with the view that accumulation of debris in Bruch's membrane is a non-specific age change. However, it is unlikely that the failure involves isolated metabolic systems alone, since there is considerable clustering of data. It is more likely that the changes represent the result of a spectrum of metabolic abnormalities, but that the two eyes of an individual share the same attributes.

These findings also have clinical relevance. Symmetry of drusen would explain the high risk of fellow eyes in patients with unilateral visual loss when compared with the risk in a patient with bilateral drusen.[18,22,27,28] The number and type of drusen are important in determining the magnitude of risk,[18,22,26-29] so that the circumstances which caused the complication in one eye would also pertain in the fellow eye. Moreover, it has been shown that the attributes of drusen determine the nature of the lesion causing visual loss.[21] On this basis one would predict that the similarity of drusen between two eyes would result in symmetry of the precise complication of age related macular disease. In one study such symmetry was found.[30]

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British Journal of Ophthalmology, 1990, 74, 183–185

# Ultrasonographic measurement of uveal melanoma thickness: interobserver variability

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## Abstract

**We retrospectively reviewed ultrasonographic data on 32 uveal melanomas that had been studied both at a referral institution and at our centre within a six-week period. Generally there were good correlations between ultrasonographic measurements of tumour thickness. The mean absolute difference in ultrasound measurements of tumour thickness was 0·64 mm (range 0–2·2 mm); the mean tumour thickness was 5·2 mm (range 3·5–10·2 mm). Tumour diameter, location, the relative ultrasonographic experience with uveal melanoma, type of equipment, and tumour thickness all affected the interobserver variation of measurement.**

Measurement of uveal melanoma thickness is important in the choice of therapy, prediction of radiation complications, and monitoring the efficacy of treatment.[1] We and others have previously studied the accuracy of ultrasonographic measurement of uveal melanoma elevation in a single institution.[2-4] We observed that multiple measurements of the same tumour in the posterior pole had a variation of less than 0·5 mm, and there was an excellent correlation between ultrasonographic and clinical estimation of tumour height.[2] The accuracy of ultrasonographic measurements of tumour thickness of the same tumour in different centres is unknown. This issue is germane to the conduct of multicentre trials of uveal melanoma treatment. Tumour elevation is one of several measurements used in the choice of treatment, and it has been shown to be an important prognostic parameter for both radiation complications and survival.[5,6]

The interobserver variability of tumour measurements with the same or different ultrasound instruments is uncertain. We have reviewed ultrasonographic data on 32 uveal melanomas that had ultrasonography performed by both the referring institution and us within a six-week period. We observed that tumour thickness and diameter, the experience of the ultrasonographer, the type of equipment, and anterior location of tumour all affected the interobserver variation in the measurement of tumour thickness.

## Materials and methods

We retrospectively reviewed all charts of patients with uveal melanoma who had been referred to one of us (DHC) for therapy. Those cases that had been referred with photographic documentation of ultrasonographic studies were selected for further investigation. Criteria for inclusion in this analysis were uveal melanomas not involving the iris that had complete clinical, photographic, ultrasonographic (immersion B scan and Kretz standarised A scan) data from our institution, and ultrasonographic data that had been performed within six weeks prior to our examination from the referring institution.

All ultrasonographic studies performed at our institution were done with both immersion B scan (Sonometrics model 150, New York) and standardised A scan (7200 MA Kretztechnique, Vienna, Austria). The scanning techniques used with these two instruments have previously been published.[7,8] All patients were first studied with a 10 mHz focused B scan probe to find the maximum tumour thickness, and then had a standardised A scan performed with an unfocused 8 mHz transducer.

All outside scans were performed by a single individual in each centre with experience in ultrasonography. In 16 cases Kretz standardised A scans had been done at the referring institution, and those ultrasonographers had participated in a training course at the University of Iowa. Seven cases were studied with standardised Biophysic A scan. Nine patients were referred from the University of California at Los Angeles, seven from Denver, three from Salt Lake City, three from the University of Southern California, and one each from a number of other centres. Each centre was poled to determine the number of uveal melanomas studied by ultrasound each year in that centre.

We reanalysed all ultrasound data, and the standardised A scan measurement of tumour thickness was defined as the distance between the anterior tumour spike and the anterior scleral spike in microseconds multiplied by 0·766 to obtain tumour thickness in millimetres. This value was chosen as a composite velocity factor for the entire intraocular path of an ultrasound beam. If the anterior tumour spike could not be visualised, the anterior retinal surface spike was used. As a separate control in all cases that had both A and B scans performed these data were separately analysed for measurement inconsistencies; no case showed a marked variation between these two techniques that would have suggested a sampling error. In cases that did not have standardised A scan performed at outside institutions the B scan measurements, usually digitally displayed, were used for tumour thickness, and compared with the non-standardised A scan data. B scan data were analysed with a velocity of both 1532 m/s and 1550 m/s.

All patients in this investigation were studied prior to either $^{125}$I brachytherapy or charged particle (helium ion) irradiation. Statistical analysis was performed by both univariate and multivariate analysis. The covariates used in the analysis included tumour location (distance from nerve, fovea, and relationship between the anterior edge of the melanoma and the equator of the eye), clinical tumour diameter, tumour thickness (measured by ultrasound), type of ultrasound equipment used, the institution where ultrasonography was performed, and interval between ultrasonographic examinations.

## Results

All patients were studied prior to radiation therapy. Eighteen patients received helium ion irradiation and 14 received $^{125}$I brachytherapy. Ultrasonographic tumour characteristics are summarised in Table I. The mean tumour thickness, measured with Kretz A scan in our laboratory, was 5·2 mm (range 3·5–10·2 mm). The average of the ultrasound tumour thickness measurements performed at the University of California, San Francisco, was 0·25 mm larger than those from other institutions. The mean absolute difference in ultrasound measurements of thickness was 0·64 mm between the referring unit and our unit (Fig 1; range 0–2·2 mm; sd 0·60 mm). As shown in Figure 1, large differences in ultrasonographic measurements were observed in both large and small tumours, though there was a trend towards larger differences in larger tumours. The average time between measurements was three weeks, with a maximum of six weeks.

Twenty-three tumours were classified as medium size melanomas (3–5 mm in thickness and 10–15 mm in diameter). Nine patients had large melanomas (>5 mm in thickness and/or >15 mm in diameter); six melanomas were over 15 mm in greatest diameter. Tumour locations in the eye are shown in Table I. Fifteen patients had tumours confined to the posterior pole. Seven patients had tumours that were entirely anterior to the equator, and 10 patients had tumours that involved the choroid both anteriorly and posteriorly to the equator. Two tumours involved the ciliary body. No iris melanomas were included in this series.

The correlation between the ultrasound measurements from referring institutions and our own was 0·89. A number of factors affected these correlations. There were greater differences in ultrasound measurements from centres that examined fewer (<20 per year) versus more uveal melanomas (0·80 mm versus 0·40 mm), tumours with the anterior edge anterior to the equator (0·85 mm versus 0·47 mm), institutions that did not use Kretz standardised A scan techniques (0·50 mm versus 0·80 mm), and studies performed on progressively larger tumours (1·00 mm versus 0·50 mm). The correlation between the variations in ultrasound measurement of tumour thickness and increased tumour height were significant ($r=0{\cdot}524$; $p<0{\cdot}002$) (Fig 1). Thicker tumours were more likely to have a greater difference in ultrasonographic measurements than thinner tumours. A low level of correlation was noted between the time interval between the two ultrasound studies and the difference of thickness measurements (Fig 2).

TABLE I *Uveal melanoma location*

| *Tumour characteristics* | | |
|---|---|---|
| *Location* | | *Number of tumours* |
| Posterior to equator | | 15 |
| <3 mm nerve and fovea | 7 | |
| ≥3 mm nerve or fovea | 8 | |
| Involving both anterior and posterior choroid | | 10 |
| Anterior to equator, not involving ciliary body | | 5 |
| Involving ciliary body | | 2 |

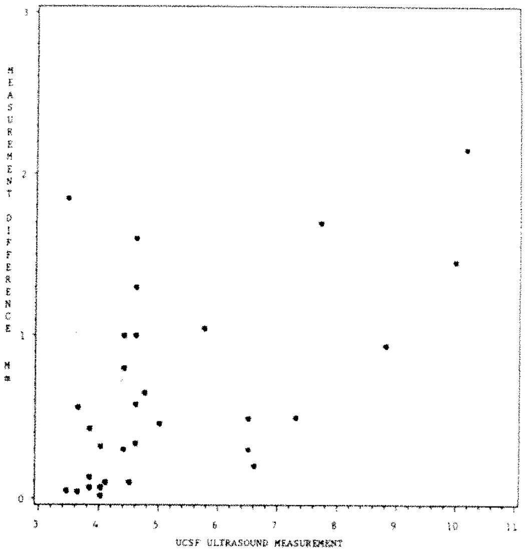

*Figure 1: Range of absolute ultrasound differences in tumour thickness measurements between different institutions. (UCSF=University of California, San Francisco.)*

We reanalysed the five cases that had the largest discrepancies (>1·3 mm) between the referring unit's and our ultrasound measurements. All were tumours over 11 mm in diameter and at least partially involved the area anterior to the equator. Three extended anterior to the ora serrata, and two had clinically obvious breaks in Bruch's membrane. All of these cases were referred from centres that examine fewer than 10 melanomas a year, and only one had been studied with standardised A scan.

We studied mathematical models to investigate factors that lead to variations in the absolute differences between interinstitution ultrasound measurements. A general linear model was fitted with the ultrasound absolute differences as the dependent variables. Several data points with the

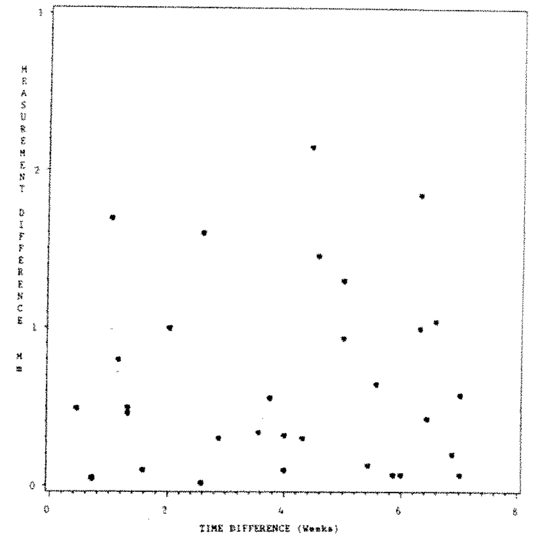

*Figure 2: Minimal correlation between variation in tumour thickness measurement and the interval between the ultrasonographic measurements.*

TABLE II *Ultrasonographic tumour characteristics*

| *Variable* | *Ultrasonographic characteristics* | | | |
|---|---|---|---|---|
| | *Minimum* | *Maximum* | *SD* | *Mean* |
| Largest tumour diameter (mm) | 5·5 | 16·0 | 3·1 | 11·1 |
| Ultrasound height (UCSF*) | 3·45 | 10·15 | 1·84 | 5·17 |
| Ultrasound height (other centres) | 3·00 | 8·50 | 1·49 | 4·91 |
| Difference in ultrasound height | −1·85 | 2·15 | 0·85 | 0·25 |
| Absolute differences | 0·02 | 2·15 | 0·60 | 0·64 |
| Time between measures (months) | 0·01 | 1·41 | 0·50 | 0·91 |

*University of California, San Francisco.

largest differences were overly influential, and when these data points were excluded the model changed significantly. This effect was minimised, and the observations were symmetrised, when the square roots of the absolute differences were used as the dependent variables. Using the general linear model with covariates listed in the 'Methods' section resulted in a best subsets model as follows (standard errors for the estimates are given in parentheses):

$$\sqrt{\text{Differences}} = \underset{(0{\cdot}032)}{0{\cdot}085\,(\text{ultrasound})} + \underset{(0{\cdot}016)}{0{\cdot}024\,(\text{diameter})} - \underset{(0{\cdot}13)}{0{\cdot}21\,(\text{number of cases})}$$

Ultrasound equals the ultrasound measurement taken at our oncology unit, diameter equals the tumour's largest diameter, and number of cases is an indicator variable for relative melanoma experience at referring centres. None of the other covariates had $t$ statistics larger than 0·80 except the time between the measurements, which had an associated estimate of 0·12 with a standard error of 0·11. The mean square error was 0·102. The model was selected in an exploratory fashion with numerous possible covariates, and the model may therefore not be generally applicable. These data suggest that larger differences in ultrasonographic measurements of tumour thickness between centres can be expected in thicker tumours, those with larger diameters, and when ultrasonography is performed in centres that examine relatively few melanomas a year. In this data set the location of the tumour was confounded with tumour size and centre experience, so that a specific parameter was not separately analysed in our model. This mathematical model serves two purposes. One, the parameter estimates suggest the degree ultrasonographic measurements vary as the covariates change. Two, it is a first approximation to estimate expected measurement differences for observations having specific covariates.

## Discussion

A number of factors influence the accuracy of ultrasound measurements of uveal melanomas. Several publications have addressed some of these issues when ultrasonography is performed in a single institution.[2-4] In most cases the variation is less than 0·5 mm in melanomas confined to the posterior pole. However, measurement discrepancies may increase in anterior lesions, those with an uneven surface topography (especially if an isolated break in Bruch's membrane is present), or if shifting subretinal fluid is present over the tumour.[7] For thicker tumours with a steep rise that are measured with standardised A scan it is essential to have the probe perpendicular to the tumour surface, since measurements obtained even slightly off axis result in errors. Even when a B scan is done before A scan measurements, in larger lesions it is still possible to fail to sample the thickest part of the melanoma, especially if there is only a small off-centre or multiple asymmetric breaks in Bruch's membrane.

Technical factors may also lead to measurement errors.[9] In this study we noted that the mean difference between measurements was approximately 0·7 mm; the mean difference decreased to approximately 0·5 mm in smaller posterior melanomas, especially when measured by experienced observers with standardised A scan. The degree of difference between institutions was less than we expected. In a single institution Nicholson and coworkers noted that, when two ultrasonography technicians from the same laboratory independently measured previously performed scans, approximately 90% were within 0·4 mm of each other with a standard deviation 0·2 mm.[4] These data suggest that attempts further to decrease the interobserver, interinstitution variation would be unlikely to be successful.

Peyster and colleagues studied the accuracy of ultrasound and computed tomography (CT) in the measurement of tumour thickness, and their finding may have relevance, especially for multicentre trials.[10] They noted a close correlation between these two measures of tumour thickness ($r=0{\cdot}92$). An obvious advantage of CT studies is that they are automated, unlike ultrasound, and therefore the measurement of tumour thickness is more likely to be consistent even in less experienced centres. While in general there was good correlation between centres in our study, some marked differences were noted. In one case the two measurements varied by over 2·0 mm. Since these larger differences could lead to inaccurately planned radiation therapy, it is imperative to restudy all cases prior to treatment, and if a marked difference is noted between the clinical and ultrasonographic measurement, to confirm the tumour size with either computed tomographic or magnetic resonance imaging.

This work was supported in part by NIH grant EYO 7504, American Cancer Society Grant PDT-321, and unrestricted grants from That Man May See, the Beal Foundation, Marvin Mintz, and the Weltkunst Foundation.

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British Journal of Ophthalmology, 1990, 74, 186–187

MINI REVIEW

# Some recent developments in ophthalmic pathology

Pathology as it is generally understood has to do with the study of disease in the laboratory and can be expressed in many ways. More and more the techniques of immunohistochemistry and molecular and cell biology have been added to the established methods, and their potential has not been ignored in the particular context of ophthalmic pathology.

One area to have benefited from the application of these newer approaches has been the study of proliferative processes in the retina and vitreous. Cell culture of epiretinal membranes, followed by staining with antigen-specific labelled antisera, has allowed the recognition of three types of cell: glia, fibroblasts, and retinal pigment epithelium.[1] The relative proportions of these cells in a given membrane varies, but in-vitro testing of their individual contractile propensities indicates that the capacity for traction is predominantly attributable to the fibroblast element. Inflammatory factors appear to be of paramount importance in the pathogenesis of the membranes and related proliferative vitreoretinopathy, with macrophages having a key role.[2] Such information concerning the nature and behaviour of what is essentially scar tissue opens up the prospect of pharmacological control, and already there have been some encouraging developments with respect to the use of sodium butyrate and certain other inhibitors.

A whole host of factors relating to proliferative and reparative phenomena within the eye have been described. Of particular relevance to retinal pathology is the identification of various substances able to stimulate neovascularisation and their specific demonstration in eyes with proliferative diabetic retinopathy. Polypeptides of differing sizes have been isolated, some closely similar, if not identical, to fibroblast growth factors, but also described is a factor specific for the endothelium of small blood vessels that weighs less than a few hundred daltons.[3] Experimental work has demonstrated a marked increase in the level of the latter substance within the retina and vitreous in response to artificially induced retinal ischaemia.[4,5] The retinal pigment epithelium also appears to be associated with the elaboration of factors able both to stimulate and to inhibit angiogenesis[6,7] and it would seem that the level of vascularisation in health is very finely tuned.

There has been renewed interest in the origin and function of the spindle cells seen in the vanguard of the developing retinal vasculature, the numbers of which are considerably increased in the retinopathy of prematurity. Commonly regarded as primitive angioblasts, there is now evidence, based on a positive reaction for glial fibrillary acidic protein, that they may be a type of astrocyte.[8] Moreover, irrespective of their histogenesis, an increase in the number of intercellular gap junctions has been reported in the retinopathy of prematurity,[9] and it has been speculated that such spindle cells may be the source of the angiogenic stimulation in the proliferative phase of the disorder.[10]

Still on the subject of cell proliferation but changing the terms of reference to neoplasia: a better understanding is slowly emerging of so-called pseudotumours of the orbit. These are lymphocytic lesions of unknown aetiology with hyperplastic germinal centres, presumed to be inflammatory and typically associated with a good response to corticosteroid therapy. There are, however, those cases in which the biopsy findings are equivocal, and it constituted a real advance when the application of immunohistochemical techniques made it possible to distinguish between monoclonal and polyclonal lymphoid proliferations.

Monoclonal disorders are recognised by the replication of seemingly identical cells derived from a single aberrant mutation. They can be recognised in the context of B cell disorders, which account for virtually all orbital lymphomas, by their restriction to the production of just one type of antibody with a single type of light chain. The inference is that such lesions are neoplastic, while those characterised by more than one sort of antibody are deemed to result from the reactive proliferation of an array of lymphocytes. Undoubtedly this has made for more accurate diagnosis, but still there are problems because occasional polyclonal lesions have been observed to disseminate. However, on the basis of gene rearrangements, the application of DNA probes has revealed that clones of mutant neoplastic cells can be embedded within lesions of this sort,[11] suggesting that the lymphoid disorders of the orbit constitute a continuous spectrum from unquestioned inflammatory processes to frank lymphoma. If this proves to be the case, 'pseudotumours' of the orbit will probably come to be seen as manifestation of the mucosa associated lymphoid tissue (MALT) concept described in other areas of the body and so having an inherent if limited capacity for malignant transformation from the outset.

Study of the genetic abnormality in retinoblastoma has also been fruitful. Consequent on the mapping of the presumed defective gene on the long arm of chromosome 13 (13q14) other work has shown that tumorigenesis is linked to deletion of a gene at this position and not to altered gene behaviour. In other words the putative retinoblastoma gene behaves as an oncogene suppressor or antioncogene. It also appears that both allelic genes need to be deleted before a neoplasm ensues,[12] which nicely conforms with the 'two hit' hypothesis formulated by Knudson[13] to account for the inheritance of retinoblastoma. Other work, based on cell culture and immunocytochemistry, indicates that the tumour arises from a cell with potential for both neural and glial differentiation,[14] even though it is the former option that is usually expressed.[15]

The endothelial cells lining the trabecular tissue of the anterior chamber subserve several functions, including control of trabecular core hydration, glycosaminoglycan formation, and phagocytosis of cellular and other detritus reaching the outflow system. Their loss compromises drainage efficiency and may prove to be the single most important event in the pathogenesis of primary open angle glaucoma, since the normal age-related reduction in cellularity appears to be enhanced in this condition.[16,17]

One of the more telling advances in the field of ocular immunopathology has been the demonstration that the surfaces of retinal vascular endothelial cells may bear normally covert class II major histocompatibility antigens,[18] because this suggests that such cells can be involved in immune processes affecting the retina. The combination of local ocular antigens and class II HLA antigens on the cell membrane could serve to bind circulating activated CD4+ T cells[19] and could account for the perivascular accumulation of lymphoyctes commonly seen in retinal inflammation. The knowledge that activated T cells are responsible for perpetuating the inflammatory process in uveitis has led to the beneficial application of immunosuppressive drugs such as cyclosporine which specifically target these cells.[20]

ALEC GARNER

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British Journal of Ophthalmology, 1990, 74, 188–191

CASE REPORT

# Ptosis as the early manifestation of pituitary tumour

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**Abstract**

**Three patients who developed unilateral ptosis followed by partial third nerve palsy were found to have a pituitary tumour. The visual field defects were minimal and asymptomatic. Two patients had a chromophobe adenoma and one patient had a prolactinoma. The importance of recognising a pituitary tumour as the cause of acquired unilateral ptosis is emphasised.**

Loss of vision and visual field are the predominant ocular symptoms of pituitary tumour. In 1000 cases of pituitary tumours reported by Hollenhorst and Younge,[1] 613 patients had visual symptoms; 421 of them had loss of vision as their presenting complaint.

Pituitary adenomas cause disorders of eye movements even less commonly than they produce loss of vision and visual field, and those disorders usually occur late in the course of the disease.

We now report three cases which presented with the main complaint of unilateral ptosis due to pituitary tumour.

## Case reports

### CASE 1

A 30-year-old woman was admitted to the neurology section of the Veterans General Hospital on 10 April 1985 with the main complaint of ptosis of the right eye for 10 days. The ptosis had begun suddenly on 1 April. The course of the ptosis fluctuated, being better in the morning and worse with fatigue, and then improving. Because the Tensilon (edrophonium) test was negative she was sent for a neuro-ophthalmological consultation on 13 April 1985. Examination showed her visual acuity was OD 20/30 −9·0 DS/−2·50 DC×180; OS 20/30 −9·0 DS/−2·50 DC×180. She could read 15 out of 15 Ishihara colour plates with each eye. The pupils measured 3 mm in the right eye and 4 mm in the left eye, and reached normally to light. No afferent pupillary defect could be detected. The palpebral fissure was 6·5 mm on the right and 10 mm on the left (Fig 1). There was 25-prism dioptre exophoria on near fixation and 25-prism dioptre exotropia on far fixation. Mild limitation of the right medial rectus muscle was noted. Both fundi were normal. Goldmann visual fields showed bitemporal hemianopia on I2e target (Fig 2). A pituitary tumour with partial third nerve palsy was diagnosed. A routine x-ray of the skull was normal, but a CT scan of the brain showed an enlarged pituitary fossa with marginal enhancement, which was compatible with pituitary adenoma.

The patient underwent trans-sphenoid hypophysectomy on 7 May 1985. The visual fields became full and the oculomotor palsy disappeared one week after the operation (Fig 3). The tumour was a chromophobe adenoma, diffuse type.

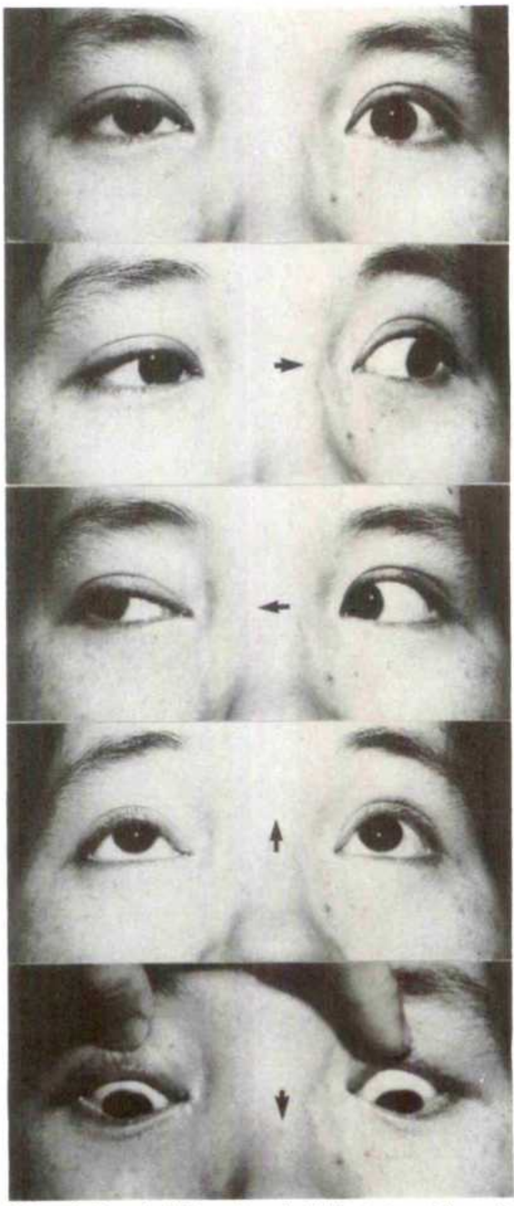

*Figure 1: Case 1. Mild ptosis and mild limitation of the medial rectus muscle of the right eye were noted preoperatively.*

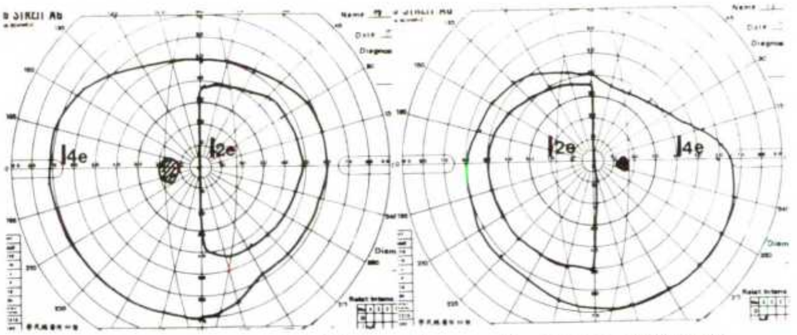

*Figure 2: Case 1. Goldmann visual fields showed bitemporal hemianopsia on I2e target.*

### CASE 2

A 62-year-old man presented on 12 April 1985 with the main complaint of ptosis of the right eye for a few days. An ophthalmic examination showed visual acuity with the best correction was OD 20/25 and OS 20/20. He could read 15 out of 15 of Ishihara colour plates with each eye. The palpebral fissure was OD 7 mm and OS 10 mm (Fig 4). On both sides the pupil size was 3 mm, with normal light reactions, and the extraocular movements were normal. The edrophonium test was negative. The Goldmann visual fields showed bitemporal upper sector defects on I2e target (Fig 5). A pituitary tumour was diagnosed. A partial right third nerve palsy then developed progressively while the patient was waiting for a CT scan. The scan of the brain showed a lobulated sellar mass with suprasellar extension, more on the right side. The patient underwent trans-sphenoid hypophysectomy. The tumour was a chromophobe adenoma. The oculomotor palsy and visual field defects were found on postoperative follow-up to be cured.

### CASE 3

A 61-year-old man came on 23 February 1988 with the main complaint of sudden onset of ptosis of the right eye on 9 February. Senile cataract in both eyes had been diagnosed several months previously. His vision with best correction was 20/70 in each eye. He could read 15 out of 15 of Ishihara colour plates with each eye. The palpebral fissure was OD 3·5 mm and OS 8 mm (Fig 6). The pupil size was OD 4 mm and OS 3 mm, with normal direct and indirect light reactions. No relative afferent pupillary defect could be detected. There was limitation of the medial rectus of the right eye. The lenses were moderately opaque. The fundi were normal. Goldmann visual fields with small target examination showed temporal upper sector depression on the right and a normal result on the left (Fig 7). A CT scan of the brain revealed a sellar mass with right suprasellar extension. A hormone study revealed prolactin 987 µg/l (normal <22). The patient underwent craniotomy. Histologically the tumour was found to be a prolactinoma. Postoperative follow-up showed the oculomotor palsy was improving. In July 1988 the patient suffered from headache and bitemporal hemianopia, when a CT scan of the brain showed a recurrent tumour. But this time no oculomotor abnormalities were found.

## Discussion

Pituitary tumours may produce a variety of symptoms, depending on their direction of

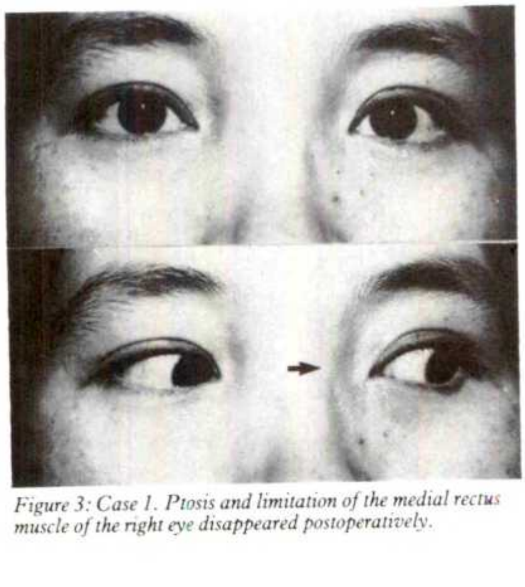

*Figure 3: Case 1. Ptosis and limitation of the medial rectus muscle of the right eye disappeared postoperatively.*

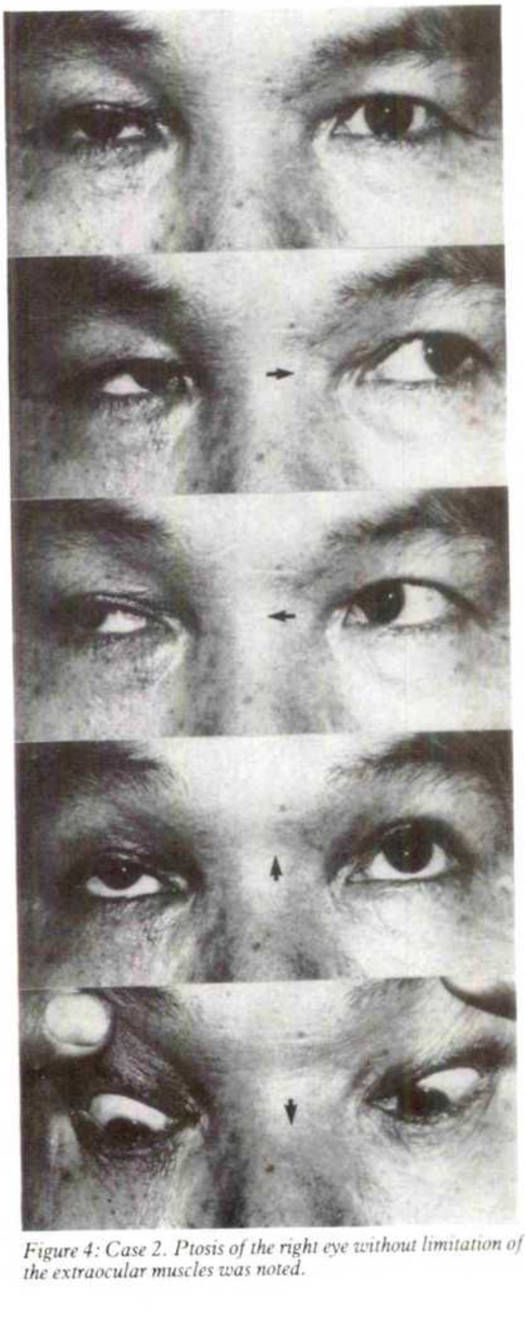

*Figure 4: Case 2. Ptosis of the right eye without limitation of the extraocular muscles was noted.*

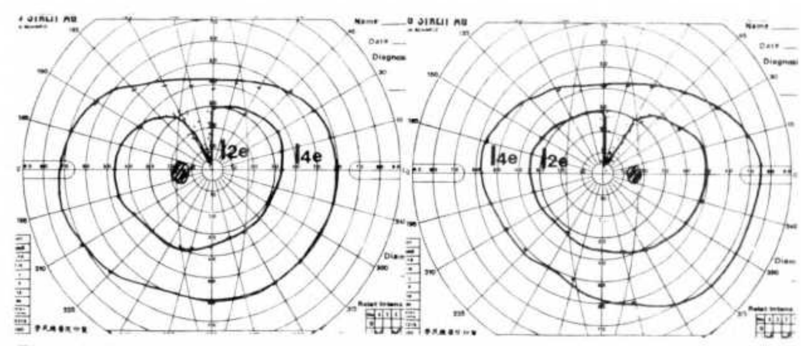

*Figure 5: Case 2. Goldmann visual fields showed bitemporal upper sector defects on I2e target.*

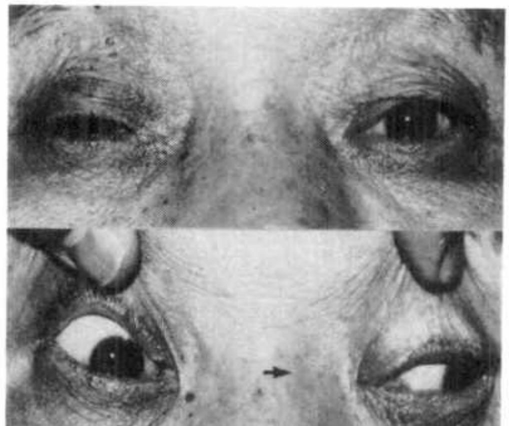

*Figure 6: Case 3. Ptosis and limitation of the medial rectus muscle of the right eye were noted.*

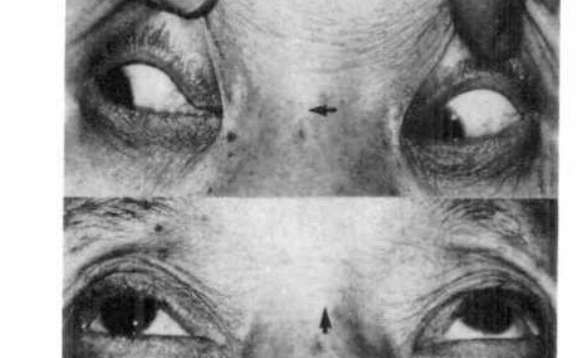

*Figure 7: Case 3. Goldmann visual fields revealed temporal upper sector depression on the right eye and normal on the left eye.*

growth. As they increase in size the first structure they compress is the chiasm. An ocular nerve palsy resulting from encroachment on the cavernous sinus is less common but has been reported in 1–6%[1-4] of patients with pituitary tumours.

Although oculomotor palsies may occur in isolation, they generally develop as the end stage of a pituitary tumour, and are combined with loss of vision or visual field.

With lateral extension of the tumour there is involvement of the oculomotor, troclear, and abducens cranial nerves because of their proximate location in the cavernous sinus. The oculomotor nerve is most frequently involved.[5] Occasionally the first and second divisions of the trigeminal nerve may be affected.

Robert *et al*[5] noted that in cases of ocular palsy occurring with pituitary tumours, of all the muscles supplied by the third nerve the levator palpebrae superioris was the most commonly affected, as shown by partial or complete ptosis.

The oculomotor nerves arise from a group of nuclei at the level of the superior colliculus. Crossed and mainly uncrossed fibres course through the red nucleus and the inner side of the substantia nigra to merge with the sella turcica in the outer wall of the cavernous sinus and, through the superior orbital fissure, to supply the medial, superior, and inferior rectus muscles and the inferior oblique and levator palpebrae muscles.

The topographic arrangement of the fibres within the oculomotor nerve in the cavernous sinus is unclear. Our patients developed ptosis in the early stages of oculomotor palsy, which suggested an effect on the fibres going to the levator palpebrae muscle located superficially in the medial portion of the nerve within the cavernous sinus.

Several mechanisms have been proposed as causing oculomotor palsy.[6-10] The tumour may transmit pressure to the wall of the cavernous sinus.[7] Or it may break through the wall of the cavernous sinus and directly compress the nerve[9] or its blood supply.[10] Because the trans-sphenoidal approach was used, it was impossible to tell if the cavernous sinus was compressed or invaded.

Most of the tumours causing ocular palsy are chromophobe adenomas.[5] This tumour is almost never diagnosed before it has grown large enough to compress the anterior visual pathways, causing field defects.

Prolactinoma is not normally considered as a cause of third nerve palsy. Most patients with prolactinoma do not have neurological or visual symptoms or signs, because the tumour is still relatively small when it is discovered. A review of the literature revealed one case of prolactinoma presenting with intermittent isolated third nerve palsy[11] and one presenting with fifth and sixth cranial nerve palsy.[12] Our third patient presented with partial third nerve palsy and a mild field defect in one eye, which is also unusual.

All three of our patients sought medical advice for ptosis. The cases are a reminder that patients with acquired ptosis need detailed neuro-ophthalmological examination.

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# BOOK REVIEWS

**Prevention of Eye Disease.** Edited by Mitchell H Friedlaender. Pp 192. No price given. Mary Ann Liebert: New York, 1988.

The Francis I Proctor Foundation, University of California, and its affiliate the Alta California Eye Research Foundation, have pioneered research and training in the important and increasingly recognised field of prevention of eye disease. This publication is a welcome addition to a slowly increasing library which attempts to include a wider world view. Thirty-one authors present contributions on many subjects, including bacterial, viral, fungal, and parasitic infections, ophthalmia neonatorum, ocular injuries, contact lens-induced disease, uveitis, endophthalmitis due to drug abuse, iatrogenic drug-induced eye disease, and vaccines. Each chapter concludes with references and some of these give comprehensive lists for referral. Some contributions reflect more particularly the North American and developed world scene. However, the shared experience of improved ophthalmic practice and care, for example in prevention of ocular injuries and iatrogenic eye disease, has significant application worldwide. Other chapters, such as those on nutritional blindness and prevention of blindness, have special reference to the developing world.

It should be noted that for children aged 1 to 6 years with vitamin A deficiency the World Health Organisation recommends 200 000 IU of vitamin A orally on day 1 and day 2, with a further single dose four weeks later (half doses are given to children under 1 year old). Women of reproductive age, whether pregnant or not, with night blindness or Bitot's spot, should have only 10 000 IU daily for no more than two weeks. Ivermectin (Mectizan) is bringing fresh hope and impetus in the treatment of onchocerciasis. Trials are at present being conducted.

The text of this book is easily read, informative, and provides recent advances and views on a variety of topics, with the constraint of prevention of ocular disease as the main theme in presentation.

D D MURRAY McGAVIN

**Ophthalmic Clinical Debates.** By Thomas A Deutsch. Pp 348. £30.50. Wolfe Medical: London, 1989.

In this imaginatively written book the author presents a number of case histories of hypothetical patients with common problems whose treatment is often controversial. He then invites a number of well known authorities to discuss the cases and to suggest the best line of management. Not surprisingly, the reader is treated to differing, and at times diametrically opposed, opinions. For example, an ophthalmologist with an acute central serous retinopathy would receive immediate laser photocoagulation from Schatz, whereas Yannuzzi would follow up such a patient conservatively. A myopic librarian with bilateral cataracts would receive an 8-dioptre implant from Sinskey, whereas Jaffe would use an 18-dioptre implant. Although such conflicting recommendations may on the face of it seem confusing, the contributors both explain and argue their respective points in an informative and entertaining fashion.

This is an unusual and very readable book. I learnt a great deal from it.

Z GREGOR

**Contact Lenses in Ophthalmology.** By Michael S Wilson and Elisabeth A W Millis. Pp 152. £39.50. Butterworths: Guildford, Surrey. 1989.

This concise and readable book succeeds in its aims as an introduction both for ophthalmologists who want to know more about the applications of contact lenses and for those wishing to start fitting lenses. The introductory chapters, with frequent use of summary tables, give a clear description of contact lens terminology, the biology of contact lens wear, and lens types and hygiene. They are useful reading for newcomers to the field and will take the mystique out of contact lens practice. These chapters, taking only minutes to read, can be recommended to anyone working in general ophthalmic clinics. The optics of contact lenses are barely discussed, and, though many ophthalmologists view this subject with trepidation, a fuller discussion might further clarify indications for different lens types. Subsequent chapters on the equipping of a practice and the choice and fitting of different lenses are good but emphasise the use of polymethyl methacrylate (PMMA), which is now rarely prescribed. The complications of lens wear are dealt with separately for each lens type. This leads to duplication and loss of consistency in an area where more guidance in the diagnosis and management would be helpful. The final chapters deal briefly with the medical applications of lens use. There are useful references at the end of each chapter and a bibliography to guide the reader to alternative sources. These are well chosen and compensate for the lack of references in the body of the text. Despite these reservations it is one of the best introductory texts on contact lenses for the ophthalmologist.

JOHN DART

# LETTER TO THE EDITOR

## Use of viscoelastic agents to aid visualisation during ocular surgery

SIR,—The viscoelastic agents have been used primarily as tools facilitating surgical manipulation of tissues, tissue displacement, or as methods of filling intraocular volume. We wish to describe additional uses of these agents as optical devices to aid visualisation during surgery.

1. *To prevent opacification of the corneal epithelium.* A clear view through the cornea is essential for successful cataract and retinal surgery. It is not uncommon for the view to be obscured owing to changes in the corneal epithelium. Regular wetting with a physiological solution helps, but this may further damage the epithelium, requiring ever more frequent wetting. In addition this wetting has to be performed regularly by an assistant. Application of a thin layer of hydroxypropylmethylcellulose (HPMC) at the start of the operation makes the use of wetting solutions unnecessary and also protects the corneal epithelium from the changes associated with regular wetting. This application needs to be repeated only once or twice during the operation. Full strength sodium hyaluronate is not suitable for this purpose, as it is too elastic and does not spread out over the cornea.

2. *As a temporary magnifying aid.* A collection of viscoelastic substance forms a dome shaped elevation, creating the effect of a plus/convex lens. This is useful for magnifying images from the eye. The retinal view can be improved if the pupil is small or if the only good view is through clear gaps in a cataractous lens. For this particular use sodium hyaluronate is more useful than HPMC, as it maintains its elevation for longer periods.

3. *To displace oil droplets from the cornea.* After a vitrectomy with fluid/silicone oil exchange, droplets of oil on the cornea may obscure the retinal view during indirect ophthalmoscopy. HPMC readily displaces these droplets of oil and improves visualisation.

4. *To reduce the distortion* caused by a gas/fluid interface behind a posterior capsule in a pseudophakic eye.

In addition to these uses HPMC can also be used to evacuate substances from the anterior chamber[1 2] and to reduce the distortion caused by folds in Descemet's membrane, particularly in an aphakic eye during fluid/gas exchange.[3]

In summary we wish to draw attention to the value of viscoelastic substances as optical aids during ophthalmic surgery.

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# NOTES

## Wilmer Institute endowed lectureship

Professor Fred C Hollows, chairman, Department of Ophthalmology, University of New South Wales, will deliver the third Mohammed Aziz memorial annual lecture on blindness of the tropics on 30 March 1990, at the Wilmer Institute at Johns Hopkins Hospital. The title of the lecture will be 'The prevention of blindness in the tropics'.

## Perimetric Society

The IXth International Perimetric Society Meeting will be held in Malmö, Sweden, on 17–20 June 1990. Further information from: IXth Meeting Secretariat, Department of Ophthalmology, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden.

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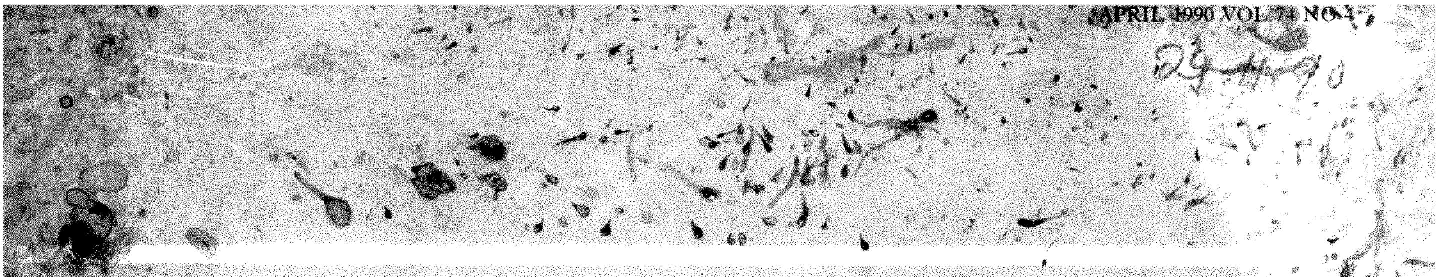

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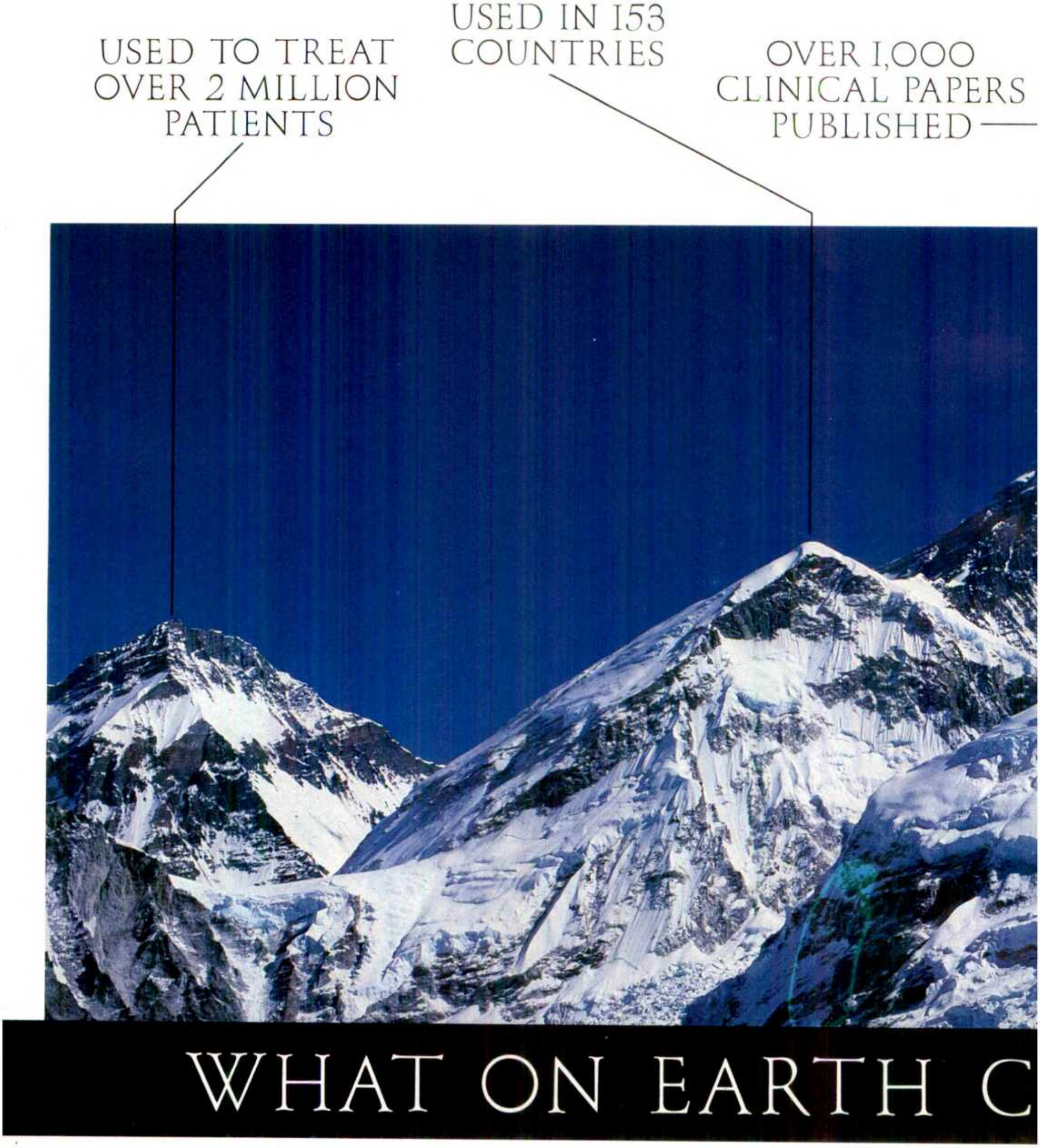
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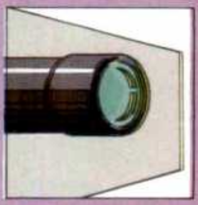

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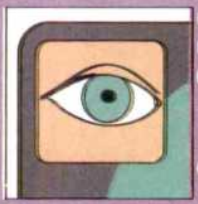

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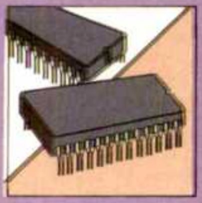

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## *Editorial*

# Are there two varieties of primary open-angle glaucoma?

In this issue we publish a paper from the Vancouver group which claims to have detected two separate 'clusters' of patients with open-angle glaucoma. We should not be too surprised at the idea because something like this has been suspected for a long time. What we should be surprised about, however, and what we should give all due credit to the authors for, is producing evidence. The evidence is based on a somewhat complex statistical analysis of various aspects of the patients' vascular systems plus their glaucoma data. Readers must consult the paper for the details and some may find the statistics hard to follow.

One of the problems about abstruse statistical methods is that non-experts cannot be certain that the claims made have been properly authenticated. The matter has to be taken on trust. The essence of the proposition is as follows. There are two populations (clusters) in open-angle glaucoma. The clusters are distinguishable from one another because in certain characteristics mainly to do with their vascular systems they have differences which can be detected by sophisticated statistical analysis. In contrast, however, they are almost indistinguishable from one another by careful studies of their basic glaucoma data, such as their pressures (equal number of high and low pressure types in the two populations), fields, discs, ages, sexes, and so on. There is, however, one very important difference between the two clusters in respect of the glaucoma data. One of the clusters shows pressure-dependent field-loss progression, whereas the other shows field-loss progression apparently independent of pressure. Even more surprising, the pressure-dependent group comprises only about one-third of all the cases of open-angle glaucoma studied.

If this is true, it is disturbing news so far as management is concerned. Moreover, it goes a long way towards explaining the disappointing results seen in long-term follow-ups of glaucoma treatment such as have been published recently. It now becomes an urgent matter for other centres to get to work to try to confirm or disprove these findings. To a certain extent it may be possible to get some clues to this fairly quickly by retrospective studies, particularly in centres with a good glaucoma data base. Even where good data are available about the glaucomatous characteristics of the patients, recall will be necessary in order to make the various medical tests suggested by Schulzer *et al.*

If the hypothesis is eventually proved, we shall have to make several changes in the way we approach and manage patients with open-angle glaucoma. Apparently no less than two-thirds of our patients will have field loss which will be non-pressure-dependent. Therefore even more energetic efforts will be needed to try to determine if the loss is dependent on something else. And these patients will require extremely sensitive counselling. We shall need to devise formulae to reassure them that blindness from glaucoma is rare in relation to the large number of persons who suffer from it and that loss of field normally occurs very slowly at an average of perhaps only about 3% a year. This should be enough to reassure most of our 60 and 70 year olds, but we shall be hard put to it to find consolation for our 40 and 50 year olds.

So far as the pressure-dependent group is concerned, the views most in favour of surgery are likely to prevail, and insistence on maximal lowering of pressure will be fully justified.

REDMOND SMITH

*British Journal of Ophthalmology*, 1990, 74, 194

## *Editorial*

# Getting an air lock on the macular hole

Anyone who has tried amateur plumbing, especially in connection with central heating, will be familiar with the power of the air lock. It is really remarkable how air is able to block the flow of water in a pipe, the lumen of which is enormous compared with the minute orifice through which air itself can pass, for example in a slow puncture of a motor tyre. It is all supposed to be something to do with surface tension, but I still regard it as one of the wonders of nature, and it puts me off trying to do the plumbing except in the most dire emergencies. Since the power of air in blocking pipes has been known for so long, and since a hole is after all only a very short pipe, it is remarkable that it took so long for the potential of air (or other gases) in the treatment of retinal detachment to be realised.

One of the minor mysteries of retinal detachment has always been the macular hole. In the days before binocular indirect ophthalmoscopy and the various slit-lamp techniques for retinal examination it was difficult to establish whether a macular hole was genuine. If the macula was flat there was less of a problem, but if it was detached the illusion of a macular hole was nearly always present when a direct ophthalmoscope was used. This led to the general belief that macular 'holes' could be ignored and the search concentrated on the rest of the retina.

With the better methods of examination now available it has become clear that true macular holes do exist and can cause retinal detachment. Nevertheless a detachment due to an isolated macular hole is still very much of a rarity. This is fortunate for several reasons, not least because some degree of central visual loss is almost inevitable even after successful retinal replacement. Destruction of the macula by photocoagulation, or by cryo or even diathermy, if the macula can be reached, has normally been attempted as part of the operation for replacement, and a number of ingenious devices for achieving an indent or buckle have been suggested over the years. It was always a struggle to place the chosen method of indentation far enough back on the eye, whether it was Rosengren's ball or solid or sponge silicone rubber, and it was particularly awkward to insert the most posterior stitches. I believe Kronlein's lateral orbitotomy was even suggested at some stage as a means of reaching far enough posteriorly on the globe.

A paper by Yoon-Kee Lai in this issue reminds us of the revolution which seems to have occurred in the treatment of detachment due to macular hole. The struggles and difficulties outlined above are now apparently things of the past. The paper does not claim that the technique is original but it is nevertheless valuable for it to be brought to our attention, since many non-specialised ophthalmologists still carry out a number of detachment procedures, and this technique should prove extremely useful in these rare cases.

It is interesting to speculate on why it has taken so long for the idea of blocking holes in the retina with intravitreal gas to catch on with ophthalmologists. There must be a number of reasons, not least of which would be the traditional reluctance of ophthalmologists in the first half of the twentieth century to have anything to do with the vitreous if they could avoid it. The vitreous was almost taboo. Other reasons were the difficulties of working out a good sequence for applying heat, light, or cryo, draining fluid, raising a buckle, and inserting gas without completely losing the ability to see what was going on inside the eye. There is some interesting correspondence on the subject in the *BJO* of November 1986,[1,2] and one of the authors concerned pointed out that in the D-ACE sequence (drainage, air, cryo, explant) the air tamponade allowed a more modest buckle to be employed than might otherwise have been needed. Macular hole tamponade carries this principle further, since in the cases described in the present paper neither buckle nor choroidoretinal burning was used.

To revert to my thoughts on plumbing expressed at the beginning of this editorial, it is indeed fortunate that air does not pass through the macular hole but, by blocking it in the same way as it blocks my central heating system when I try to tamper with it, completely cuts off the subretinal fluid from the vitreous, thus allowing rapid resorption. The remarkable thing is that no burning is needed to get the retina to adhere, though there is of course a precedent for this as was pointed out by Chignell and Markham[3] when they did a series of conventional buckling procedures without cryo, with fairly good results. Such daring surgery would not normally be advisable now for the more usual type of detachment with peripheral tears, but it is certainly well worth knowing that it is possible to get away with it in cases with a macular hole.

REDMOND SMITH

1 Urrets-Zavalia A. Treatment of retinal detachment. *Br J Ophthalmol* 1986; 70: 874.

2 McLeod D. Reply to Urrets-Zavalia. *Br J Ophthalmol* 1986; 70: 875.

3 Chignell A, Markham RHC. Retinal detachment surgery without cryotherapy. *Br J Ophthalmol* 1981; 65: 371–3.

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3. Schoene RB, Abuan T, Ward RL, Beasley CH. Am J Ophthalmol 1984 **97** 86-92
4. Van Buskirk EM. New Trends in Ophthalmol 1986 **104** 1178-1184

## *Editorial*

# Local anaesthesia for cataract surgery

I have always believed that general anaesthesia provides for the surgeon and the patient a wider margin of safety during intraocular surgery than is possible with local anaesthesia. This is because the anaesthetist is able to control the choroidal blood flow with positive pressure hyperventilation during the surgical procedure, and hence maintain a desirably soft and still eye. Despite this belief, which is widely held, general anaesthesia is increasingly regarded as an unaffordable luxury in ophthalmology, particularly for cataract surgery.

The surge in popularity of local anaesthesia for cataract surgery does not appear to have been associated with a significant rise in complications during or after the operation, though hard data are hard to come by. It even appears to be possible to achieve excellent results with less and less local anaesthetic agent and without recourse to retrobulbar or even peribulbar injection. Techniques are described which seem to be designed to produce adequate peroperative analgesia with only a nod in the direction of ocular akinesia, other than by securing the eye with a superior rectus suture.

This issue sees the publication of work by Redmond and Dallas and by RJH Smith, both papers dealing with the subject of local anaesthesia for cataract surgery. Both studies, though limited in their scope, seem to indicate that the greatly abbreviated dosage and technique should find favour. I have tried each of the described methods on an occasional and ad hoc basis without serious mishap. I could not, however, compare favourably these experiences with the security and peace of mind I enjoy with the help of an anaesthetist colleague.

Many factors are forcing us to change our ways. Socio-economic concerns promote more day case surgery, sometimes with inadequate consideration for the patients's welfare. Patients are not universally keen on the idea of going home immediately after surgery (often a journey of many miles for hospitals in London) when they have to return again for inspection next day. In the United States, where this process is the norm, hotels and motels have sprung up adjacent to the busy cataract facilities and patients are prepared and expect to pay for the use of them. Such enterprise does not exist in the UK, and NHS patients, I venture to suggest, would be unwilling to pay were it to emerge.

The fact remains that we do not know what is best. In their summary Redmond and Dallas state that their results may encourage investigation, and this is certainly needed. Only evidence from a prospective and preferably randomised study will serve to provide an answer. One should also not forget that day case surgery no longer requires local anaesthesia only. Agents and techniques for general anaesthesia are changing fast, so that rapid and safe recovery is becoming a realistic expectation. Thus may we be able to have our cake and eat it.

ARTHUR STEELE

*British Journal of Ophthalmology*, 1990, 74, 196–200

ORIGINAL ARTICLES

# Biostatistical evidence for two distinct chronic open angle glaucoma populations

Michael Schulzer, Stephen M Drance, Cedric J Carter, Donald E Brooks, Gordon R Douglas, Wing Lau

**Abstract**

**Twenty-six eyes of 26 patients with low-tension glaucoma and 34 eyes of 34 patients with high-tension glaucoma were studied. Fifty-one measurements were available on each patient, including visual field indices, finger blood flow measurements, as well as haematological, coagulation, and biochemical and rheological variables. Multivariate analysis revealed two statistically distinct groups of patients, with low and high tension glaucoma cases equally distributed in both. The smaller group (15 patients) showed a suggestion of vasospastic finger blood flow measurements, and had a high positive correlation between the mean deviation (MD) index of field severity and the highest intraocular pressure (r=0·715, p=0·0008). The second, larger group (45 patients) showed disturbed coagulation and biochemical measurements, suggestive of vascular disease, and had no correlation between the MD index and the highest intraocular pressure.**

There is increasing evidence that there may be multiple mechanisms of damage in the glaucomas. Clinically, some patients seem to derive benefit from reduction of intraocular pressure, while others continue to fail in spite of it.[1-4] A number of arguments in support of more than one pathogenetic process have been outlined.[5,6] Investigation into the nature of these processes is hampered by the difficulty in identifying clinically patients with specific mechanisms.

Potential heterogeneity in a population may sometimes be uncovered by a statistical procedure known as principal component analysis. The details of its methodology and applications are described elsewhere.[7-9] This multivariate technique is used primarily to reduce large sets of correlated data to a relatively small number of uncorrelated 'components', which can in turn be analysed more readily with little loss of information. These components, calculated from the data, are weighted sums ('linear combinations') of the original measurements. The values of the various components for each subject are calculated and are referred to as 'scores'.

The principal components are computed sequentially from the data in the order of decreasing variability of their score values across subjects. Thus, in particular, the weights selected for the first component are calculated so that the resulting scores will have the largest possible variation between individuals.

This feature of the principal component technique makes it a valuable tool for the detection of hidden clusters within a population, since such clusters, if they exist, are often best seen through the corresponding clustering of the score values of one or several of the principal components. Most commonly the first component, having the largest spread in its score values, is the most sensitive for the identification of potential clusters. Plots of scores in the first component for each subject against the corresponding scores in other components help to display the resulting clusters graphically. Statistical methods are used to determine the significance levels of apparent clusters.

Clearly, successful application of this method to the detection of a non-homogeneous population requires a representative sample and sufficient data on each subject to maximise the likelihood that relevant variables have been included.

## Materials and methods

In 1986 we planned a study to examine the vascular, haematological, and rheological differences between patients diagnosed as having low-tension glaucoma (LTG) and those suffering from high-tension glaucoma (HTG). It was decided to examine approximately 50 consecutive cases of LTG and 50 cases of HTG. These patients were studied sequentially. Some of the patients were on topical therapy and others on no treatment. The patients came from our consultation service, and included also those patients whose disease was being monitored by us on an ongoing basis.

The LTG eyes had open angles, glaucomatous abnormality of the optic discs, and characteristic nerve fibre bundle defects on Goldmann static-kinetic perimetry or static perimetry on the Oculus perimeter or on automatic perimetry (30–2 Octopus or Humphrey). Their intraocular pressure was ≤21mmHg without therapy, including pressure studies round the clock. The HTG eyes had similar disc and field changes but pressures ≥22mmHg.

In order to carry out a full-scale multivariate analysis only those patients on whom complete data (51 measurements) were available were included in this study. This led to a final sample of 26 LTG patients (mean age 61·9 (SD 12·2) years, mean intraocular pressure 19·3 (SD 1·8) mmHg) and 34 HTG patients (mean age 65·5 (SD 11·5) years, mean intraocular pressure 28·1

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(SD 4·7) mmHg). One eye was randomly selected in each patient for the analysis.

The 51 measurements which were available on each patient included three visual field indices previously defined[10]: the mean deviation (MD), which identifies the overall loss of sensitivity of points tested compared with their mean age-related normal values; the corrected loss variation (CLV), which describes the variation of threshold values between individual points tested, and provides early indication of localised field defects; and the short term fluctuation (SF), which measures the variation of all thresholds tested twice within a single field examination. In addition, the highest intraocular pressure (IOP), pupil size, visual acuity, and cup-disc ratio were recorded.

Systolic and diastolic blood pressures and electrocardiogram (ECG) (classified as normal or indicative of ischaemic abnormality) were obtained.

The blood flow in the finger and its response to heat and cold were measured by methods described elsewhere.[11] Measurements were taken of the baseline flow, flow after heating (heated flow), flow after a 10-second exposure to cold (cold flow), as well as the ratios: heated flow/baseline flow and heated flow/cold flow. The following haematological data were available: leucocyte count, red cell count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and platelet count.

In addition coagulation tests were performed after initial observations that low-tension glaucoma appeared to be associated with both cardiovascular and cerebrovascular disease, and that defective fibrinolysis was observed in patients with low-tension glaucoma.[12] The tests chosen had been shown in previous prospective clinical studies to be associated with an increased risk of vascular disease.[13] Tests included euglobulin lysis time (baseline and following ischaemic stress, and lysis time ratio of poststress to prestress),[14] factor VII, factor VIII, fibrinogen, and antithrombin III.

Measurements were also available on haemoglobin A1C, 2-hour post/food (pc) glucose, blood urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, $\alpha_1$, $\alpha_2$, $\beta$, $\gamma$ and total globulin, thyroxine ($T_4$), cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides, and the HDL/cholesterol ratio. Finally, rheological measurements included plasma viscosity and blood viscosity (peak and steady state).

### STATISTICAL METHODS

The distribution of each of the 51 variables was examined. Distributions which failed to satisfy essential statistical assumptions (stability of variance, symmetry, normality) were identified, and a correcting logarithmic transformation was applied to the corresponding measurements for the purposes of the analysis. This included the following variables: corrected loss variation (CLV), short term fluctuation (SF), visual acuity, cup-disc ratio, heated flow/baseline flow, heated flow/cold flow, euglobulin lysis time ratio, and HDL/cholesterol ratio.

A significant correlation was found between the mean deviation (MD) (see description above) and pupil size ($r=-0\cdot36$, $p=0\cdot0001$). The mean deviation was therefore adjusted for pupil size by regression analysis.

Since many of the 51 measurements were clearly correlated, a correlation matrix was calculated separately for the LTG, the HTG, and the combined LTG-HTG groups.

For the purposes of analysis, the SAS principal component analysis package was used. The data were first 'standardised', by subtracting from each measurement its corresponding sample mean and dividing by its sample standard deviation. This device allowed all measurements to participate in the analysis in an equally useful way, by removing spurious effects due to different units of measurement and to unequal variances.

In the initial stage of the computation 51 principal components were calculated, each with 51 weights ('coefficients') for the 51 meaurements anaysed. To determine which of the weights were statistically significant, the corresponding standard error for each weight had to be calculated. These standard errors are not included in the output of most computer packages available at present, and were therefore programmed in by us using the mathematical methods outlined elsewhere.[9] In this way, by progressively removing less significant weights by a method referred to as 'backward elimination', the complexity of the data was gradually reduced, retaining only those measurements which made a significant contribution to the components. The aim was to remove redundant and overcorrelated variables without degrading the precision of the statistical fit, ultimately identifying potential clusters in the sample using a minimum number of informative and significant measurements (the 'principle of parsimony').

The analysis was carried out separately on the LTG and on the HTG subgroups, and then repeated across the combined LTG-HTG sample.

In addition, 'agglomerative' analysis was also performed on these patient groups. In this approach subsets of measurements (ophthalmic, haematological, biochemical, etc.) were separately analysed into principal components. The statistically significant variables collected from the measurement subsets were then combined ('agglomerated') in various ways into a single set, which was then analysed into its principal components and progressively pared down by 'backward elimination' as described above, to a minimal number of informative measurements.

Results were compared between the various approaches. In addition, cross validations were carried out by using a randomly selected half of the individuals in the sample as the 'construction set', for which principal components were calculated, and then cross-testing the results on the remaining half of individuals in the 'validation set'.

Observed clusters were tested for the

TABLE I *Significant coefficients (weights)* in first principal component*

| *Variable* | *Coefficient of standardised variable*[†] | *Standard error of coefficient* |
|---|---|---|
| Baseline flow | 0·323 | 0·065 |
| Cold flow | 0·333 | 0·063 |
| Log (hot flow/baseline flow)[‡] | −0·373 | 0·053 |
| Log (hot flow/cold flow) | −0·370 | 0·053 |
| Prestress euglobulin lysis time | 0·324 | 0·058 |
| Poststress euglobulin lysis time | 0·312 | 0·063 |
| Glucose | 0·183 | 0·072 |
| HDL | −0·286 | 0·069 |
| Triglycerides | 0·284 | 0·069 |
| Log (HDL/cholesterol) | −0·330 | 0·064 |

*The 2-sided significance level of the glucose coefficient is 0·01. All other coefficients are significant at $p<0\cdot001$.

[†] Variables were standardised by subtracting their sample means and dividing by their sample standard deviations.

[‡] Logarithms were taken as natural logarithms.

significance of the separation between them by $\chi^2$ test on their squared standard distance.[9]

Continuous and categorical variables were compared between the generated clusters by *t* tests, $\chi^2$ tests, and methods of simple and multiple regression when appropriate.

## Results

The findings reported are based on analyses on the pooled LTG-HTG sample. Results of analyses within the LTG and HTG groups were for the most part very similar and were well summarised by the pooled sample. The intraocular pressure measurement was excluded from the analyses given here, in order to avoid confounding with the LTG-HTG classification.

Following the scheme of analyses outlined in the 'Statistical methods' section, a set of 10 significant measurements was ultimately retained. Table I lists the variables and gives the weights of the first principal component for each standardised variable, along with the corresponding estimated standard errors.

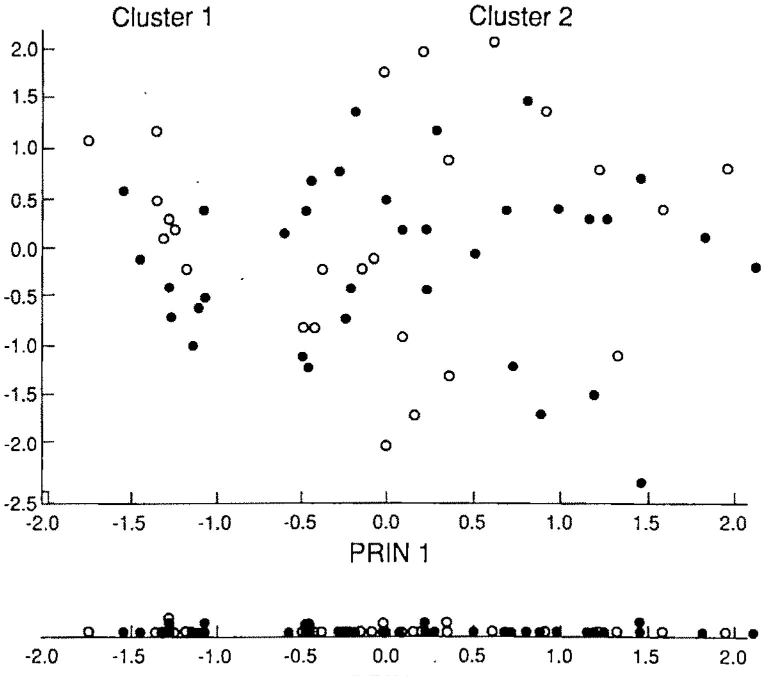

*Figure 1: Scores of the first principal component (horizontal axis), summarising the data (51 observations) on 60 eyes of 60 patients, displayed for convenience both in a pointplot and in a scatterplot against corresponding scores of the third principal component (vertical axis). Black circles represent high-tension glaucoma eyes; open circles represent low-tension glaucoma eyes. A separation into two clusters (15 and 45 eyes respectively) can be observed.*

Fig 1 shows graphically the patient scores on the first principal component (horizontal axis), displayed as a pointplot, and as a scatterplot against the corresponding scores on the third principal component (vertical axis). Similar scatterplots were obtained relating all pairs of principal components. It is clear that the information regarding potential clusters is contained mainly in the first component. Two clusters are readily seen along the horizontal axis, separated at a score value of approximately −0·8. The left-hand cluster (cluster 1) is small, consisting of 15 individuals, of whom 7 are LTG and 8 HTG. The large right-hand cluster (cluster 2) consists of 45 individuals, 19 LTG and 26 HTG. The proportions in each cluster of the LTG-HTG subgroups are clearly not significantly different ($\chi^2=0\cdot09$, $p=0\cdot77$). The observed clusters are statistically distinct ($p<0\cdot0001$). No other statistically significant clusters occur.

Table II gives the means and standard deviations in each cluster for the 10 variables identified in the final principal component, in unstandardised units. It also gives the means and standard deviations in each cluster for all other variables which showed a difference, significant at $p<0\cdot10$, between the two cluster means. The statistical level of significance for each comparison is given. No significant differences were observed in mean age (64·1 (SD 15·7) years in cluster 1; 63·8 (SD 10·4) years in cluster 2), mean highest intraocular pressure (24·7 (SD 7·0) versus 24·2 (SD 5·4)mmHg), mean pupil size (3·7 (SD 2·3) versus 3·3 (SD 1·8) mm), mean systolic pressure (117·1 (SD 18·8) versus 121·2 (SD 16·2)mmHg) or in mean diastolic pressure (74·4 (SD 8·1) versus 77·9 (SD 10·9)mmHg).

Cross-checking by other methods, as discussed earlier in the 'Methods' section, confirmed the separation into two disjoint clusters, yielding consistent results in terms of cluster variables and of cluster membership.

In order to examine the relationship between intraocular pressure and severity of the glaucomatous damage, simple linear regression of the pupil-adjusted mean deviation index (MD) of visual field severity on the highest intraocular pressure (IOP) was carried out separately within each cluster. Fig 2 and 3 show the results. A very significant correlation was found in cluster 1 ($r=0\cdot715$, $p=0\cdot0008$), indicating that the visual field loss, as measured by the MD, increased by 0·59 dB for each 1 mmHg increment in the highest IOP. No correlation was found in cluster 2 ($r=0\cdot043$, $p=0\cdot79$).

The clusters were further analysed by multiple regressions to examine the joint relationship between mean deviation (MD), intraocular pressure (IOP), and corrected loss variation (CLV) (in log CLV units) in each.

In cluster 1, where the MD and IOP were highly correlated, the MD and CLV were also significantly positively correlated ($p=0\cdot019$) after both were adjusted for the IOP. On the other hand no relationship was found between the CLV and IOP after both had been adjusted

TABLE II *Means and standard deviations of variables in the two clusters**

| *Variables* | *Cluster 1* |  | *Cluster 2* |  |  |
|---|---|---|---|---|---|
|  | *mean* | *sd* | *mean* | *sd* | *p*[†] |
| *Cluster defining* |  |  |  |  |  |
| Baseline flow | 5·68 | 4·44 | 31·04 | 20·22 | <0·0001 |
| Cold flow | 4·65 | 3·24 | 16·60 | 13·58 | 0·0014 |
| Log (hot flow/baseline flow)[‡] | 2·62 | 0·61 | 0·95 | 0·83 | <0·0001 |
| Log (hot flow/cold flow) | 2·80 | 0·51 | 1·57 | 0·79 | <0·0001 |
| Prestress euglobulin lysis time (minutes) | 253·53 | 83·19 | 513·62 | 216·08 | <0·0001 |
| Poststress euglobulin lysis time (minutes) | 138·00 | 42·63 | 382·06 | 247·75 | 0·0004 |
| 2 h pc glucose (mmol/l) | 4·42 | 1·44 | 5·80 | 3·24 | 0·0280 |
| HDL (mmol/l) | 1·40 | 0·34 | 1·03 | 0·27 | <0·0001 |
| Triglycerides (mmol/l) | 1·01 | 0·35 | 1·82 | 0·88 | 0·0010 |
| Log (HDL/cholesterol) | 0·27 | 0·07 | 0·18 | 0·05 | <0·0001 |
| *Non-cluster-defining* |  |  |  |  |  |
| MD (dB) | 12·00 | 5·76 | 8·82 | 5·80 | 0·0739 |
| Fibrinogen (g/l) | 2·81 | 0·52 | 3·13 | 0·55 | 0·0520 |
| WBC ($\times 10^9$) | 4·52 | 1·30 | 5·40 | 1·10 | 0·0126 |
| Uric acid (μmol/l) | 278·96 | 76·13 | 325·95 | 74·35 | 0·0419 |
| Cholesterol (mmol/l) | 5·24 | 0·95 | 5·78 | 0·93 | 0·0592 |
| LDL (mmol/l) | 3·29 | 0·73 | 3·85 | 0·88 | 0·0309 |
| ECG (proportion abnormal) | 0 |  | 0·44 (10/45) |  | 0·0440 |

*Included are all variables which showed a difference in the two cluster means at a 2-sided significance level of $p<0·10$.

[†] 2-Sided *t* test; for ECG, $\chi^2$ test.

[‡] Logs represent natural logarithms.

for the MD. The IOP and CLV together explained 70% of the variation in the MD measurements.

In cluster 2, where the MD and IOP were not correlated, a high correlation was observed between the MD and CLV ($r=0·70$, $p=0·0001$). As in cluster 1, no correlation could be found between the CLV and IOP.

The criterion for classifying a case into cluster 1 or 2 of Fig 1 is given in terms of raw (non-standardised) measurement units (described in Table II) as follows: for a given case the following calculation should be made: ('log' means natural logarithm): 0·01556×baseline flow+0·02578×cold flow−0·34979×log (hot flow/baseline flow) −0·40977×log (hot flow/cold flow)+0·00146×prestress euglobulin lysis time+0·00130×poststress euglobulin lysis time+0·06233×2 h pc glucose−0·87780×high density lipoprotein cholesterol+0·33127×triglycerides−0·97802×log (HDL/cholesterol)−0·2072.

When the resulting value of the criterion is negative, the case is classified into cluster 1, while a positive value would lead to classification in cluster 2. The criterion has been selected so as to minimise the chances of misclassification. In fact, it is estimated that only approximately 4·3% of cluster 1 individuals might be misclassified into cluster 2, and conversely, by this criterion.

## Discussion

Principal component analysis is an efficient, guided method for detecting potential heterogeneity in a population. As applied to a pooled sample of 60 low-tension and high-tension glaucoma patients it produced two distinct clusters, consisting of 15 and 45 members respectively. This separation was accomplished independently of the highest intraocular pressure level, with both clusters containing nearly equal proportions of low- and high-tension glaucoma patients. The two clusters were generated by the scores of the first principal component derived from 10 significant variables which were selected in stages from an initial set of 51. The final variables represented blood flow measurements in the finger under baseline conditions as well as after heating and cooling the hand, coagulation variables, and biochemical information.

The two clusters showed striking statistical

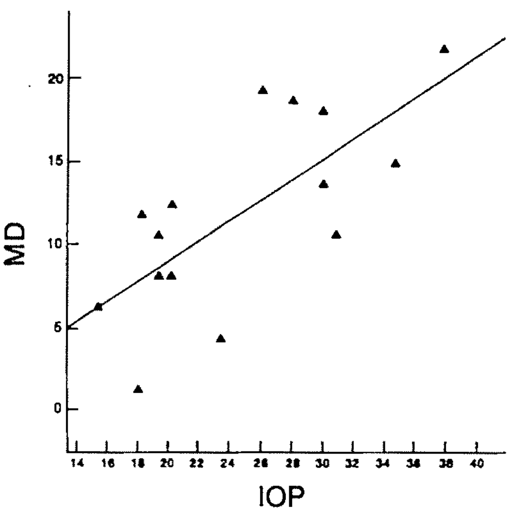

*Figure 2: Scatterplot of mean deviation (MD) against highest intraocular pressure (IOP) in the 15 eyes of cluster 1. The estimated regression line is highly significant ($r=0·715$, $p=0·0008$).*

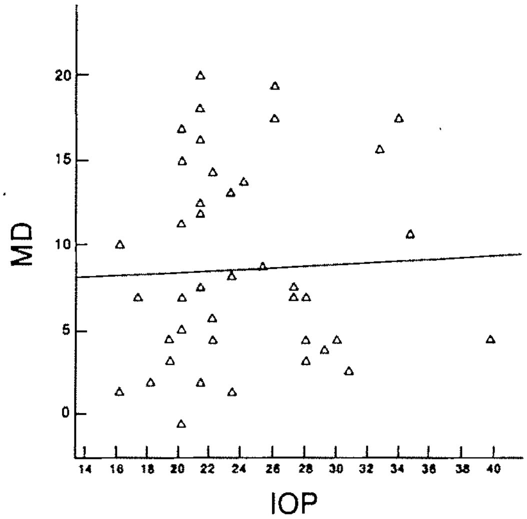

*Figure 3: Scatterplot of mean deviation (MD) against highest intraocular pressure (IOP) in the 45 eyes of cluster 2. The estimated regression line is not significant ($r=0·043$, $p=0·79$).*

differences. The smaller cluster (cluster 1) showed a lowered mean baseline blood flow level in the finger, and a lowered mean finger blood flow level after cooling, with corresponding increases in the means of the ratios of heated flow to baseline flow, and of heated flow to blood flow after cooling. These changes in blood flow in the finger in cluster 1 suggested vasospastic features. Cluster 1 showed no disturbances in any of the other measurements, and no ischaemic ECG abnormalities were noted in any individual in this cluster. The cluster was characterised by a remarkably high correlation between the degree of visual field disturbance, as measured by the mean deviation (MD), and the highest intraocular pressure of the eye (IOP) ($r=0{\cdot}715$, $p=0{\cdot}0008$). The larger cluster (cluster 2) showed no correlation whatever between the degree of visual field disturbance as reflected by the MD index and the highest intraocular pressure of the affected eyes. This cluster was characterised by raised mean euglobulin lysis times before and after ischaemic stress, with an increased post-stress to prestress ratio, increased mean fibrinogen level, higher mean 2-h pc glucose level, a lower mean HDL and higher mean LDL levels, with a lower mean ratio of HDL to cholesterol, a higher mean level of triglycerides, a considerable rate of ischaemic ECG abnormalities, as well as a higher mean leucocyte count and a higher mean uric acid level. However, the mean finger blood flow measurements in this cluster were normal, and not of the vasospastic variety.

It appears that two distinct and statistically significantly different glaucoma subgroups have been identified, raising the possibility of different pathogenetic mechanisms: a smaller group, showing vasospastic trends in finger blood flow and a strong relationship between field disturbance and highest intraocular pressure; and a larger group, showing higher means in clotting and biochemical parameters and ECG anomalies suggestive of vascular disease. The latter group showed no relationship between degree of field disturbance and the highest intraocular pressure. Group separation has been accomplished without regard to the traditional arbitrary low-tension and high-tension classification and seems to be altogether independent of the highest pressure level.

In spite of the consistency of these findings, and the support of cross validation analysis, caution in their implications must be recommended. Further testing of widely based data sets over large, representative samples cross sectionally and longitudinally needs to be undertaken to confirm and evaluate the clinical significance of these results.

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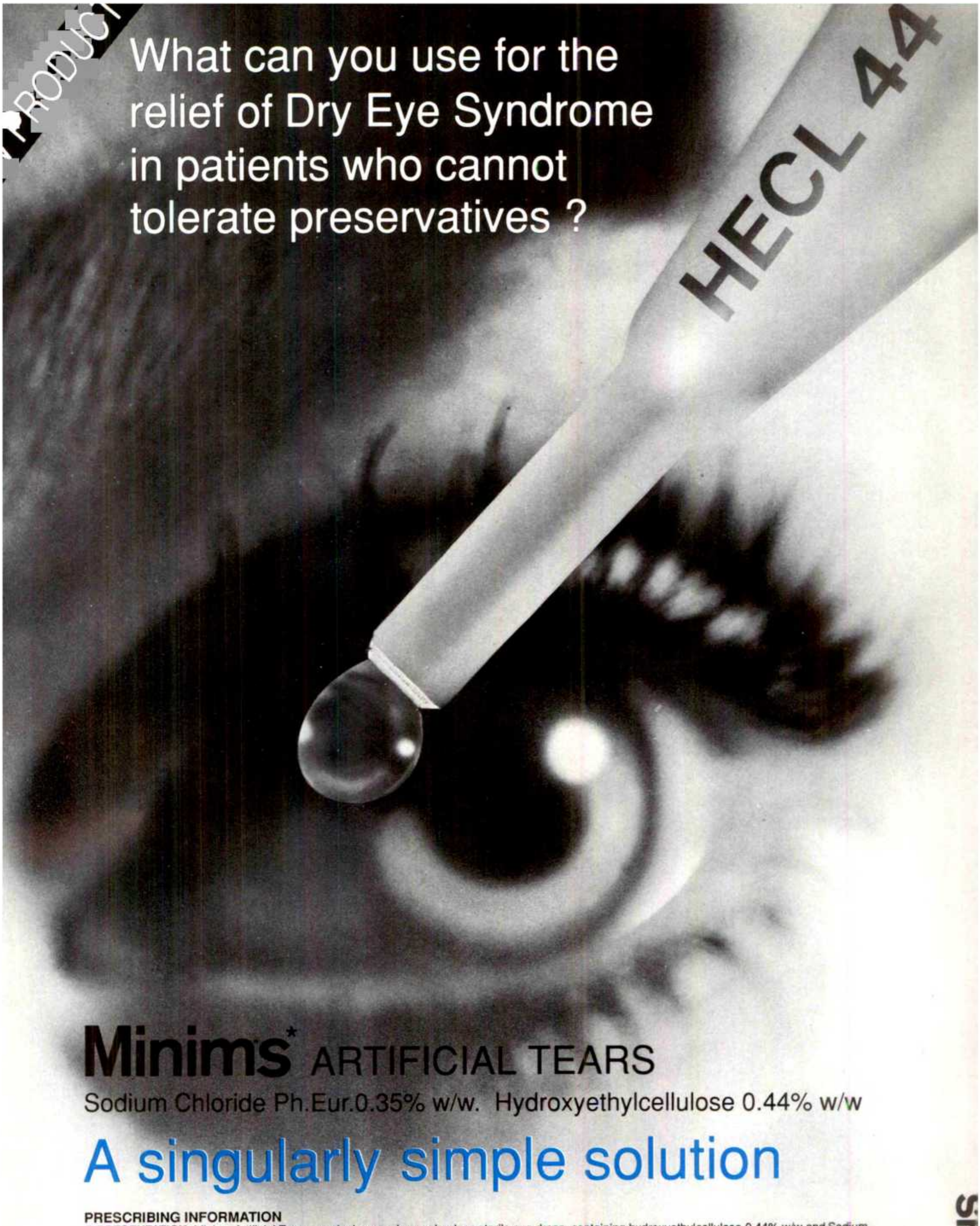
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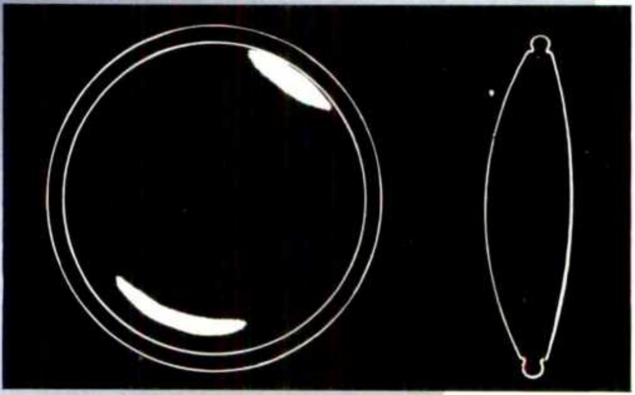

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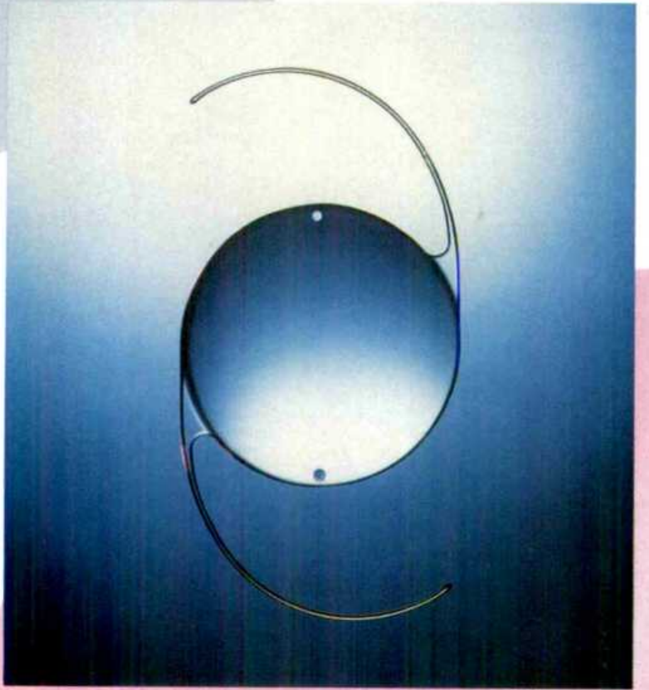

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*British Journal of Ophthalmology*, 1990, 74, 201–202

# Treatment of macular hole retinal detachment

Yoon-Kee Lai

**Abstract**

**Seven patients with macular hole retinal detachment were treated by intravitreal gas injection with or without release of subretinal fluid. Macular buckling, diathermy, cryopexy, or vitrectomy were not used. The patients were placed prone for eight hours a day until the gas had absorbed. In five of the seven patients the retina became reattached within three days and remained reattached with follow-up periods of three to 22 months (average nine months). It is believed that such detachments are due to vitreoretinal traction and the intravitreal gas bubble relieves this traction. This technique is simple, safe, and does not require costly or sophisticated instruments. It has an added advantage in preserving macular function.**

Many surgical techniques have been described for the treatment of retinal detachment due to macular holes.[1-4] These include the use of macular plombs and posterior scleral resection, with the use of diathermy, cryopexy, or photocoagulation round the macular hole to create chorioretinal adhesions. However, these technically difficult procedures have high complication rates[5] and poor visual results because of the destruction of the macula.

In 1974 Scott[6] used intravitreal silicone oil injections to flatten out 32 cases successfully. The use of silicone oil was also advocated by others.[7] Unfortunately silicone oil has definite short- and long-term complications which limits its use.[8]

In 1982 Gonvers and Machemer[9] showed that macular hole retinal detachments could be successfully treated by pars plana vitrectomy and gas tamponade without the need for inducing chorioretinal scarring, thereby preserving macular function. Another macula preserving method was introduced by Blankenship in 1984.[10] He exchanged liquid vitreous with an intravitreal gas bubble under indirect ophthalmoscopic control.

Recently Miyake[11 12] has reported a simplified method of treating macular hole retinal detachment by intravitreal gas injection with or without external release of subretinal fluid. Vitrectomy was not required, nor was cryopexy or any other form of chorioretinal destruction performed. The results of this technique in seven patients are presented in this report.

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## Patients and materials

Between November 1987 and June 1989 seven patients with macular hole retinal detachments were treated in the University Hospital, Kuala Lumpur. The inclusion criterion was that the retinal detachment was due solely to a macular hole. Any patient with visible vitreoretinal traction or preretinal or subretinal fibrosis was excluded from the study. Patients with a macular hole together with any other retinal breaks were also excluded.

There were three male and four female patients. Their ages ranged from 45 to 65 years. All were myopic; of these six had refractive errors greater than 6 dioptres. Vitreous degeneration was present in all. No case was traumatic in nature. The time from onset to diagnosis ranged from one week to three months.

Macular hole retinal detachment can be classified according to the extent of the detachment:[11]

*Type I* detachment limited to the perimacular area.

*Type II* detachment extending to equator but not to ora.

*Type III* detachment extending to ora in at least one quadrant.

Type I detachments do not require treatment. The seven patients were classified into two treatment groups based on whether they were type II or type III detachments.

There were four patients with type III detachments. These were treated in the following manner. After induction of anaesthesia (either general or local) subretinal fluid was released at the equator in the most dependent quadrant. A mixture of 50% sulphur hexafluoride was injected with a 26G needle into the vitreous via the pars plana in phakic patients or the limbus in aphakic patients. The amount injected was sufficient to reform the eyeball firmly. This amount was 1·5 ml or more in all cases. The central retinal artery circulation was checked by an indirect ophthalmoscope. The patient was then kept prone for at least eight hours a day until all the gas had been absorbed, usually between one and two weeks.

Patients with type II macular hole retinal detachments did not have release of subretinal fluid because of its posterior location. Instead an anterior chamber paracentesis was performed to soften the eye. Pure sulphur hexafluoride was then injected into the vitreous cavity in the same manner as in type III patients. The amount injected did not exceed 2·0 ml in any patient. After injection of the gas these patients were treated in the same manner as type III patients.

## Results

Five of the seven patients were successfully treated by this method. The retina became completely reattached within three days in all five patients. After complete absorption of the gas none of these patients suffered any recurrences during the follow-up period (three months to 22 months, average nine months). All five patients had improvement in their visual

TABLE I *Summary of clinical data*

| *Patient* | *1* | *2* | *3* | *4* | *5* | *6* | *7* |
|---|---|---|---|---|---|---|---|
| Age (yrs) | 64 | 45 | 65 | 57 | 60 | 55 | 53 |
| Sex | M | F | M | F | F | F | M |
| Refractive error (dioptres) | −6·0 | −20·0 | −15·0 | −1·5 | −18·0 | −10·0 | −7·0 |
| Detachment type | II | III | III | III | II | III | II |
| Duration of detachment (days) | 7 | 10 | 60 | 90 | 10 | 7 | 90 |
| Visual acuity: | | | | | | | |
| preoperative | HM | HM | HM | HM | 1/60 | HM | CF |
| postoperative | CF | 1/60 | CF | 2/60 | 6/60 | 3/60 | 6/60 |
| Success | No | No | Yes | Yes | Yes | Yes | Yes |
| Follow-up period (months) | 22 | 16 | 10 | 5 | 4 | 3 | 3 |

HM = hand movements. CF = counting fingers.

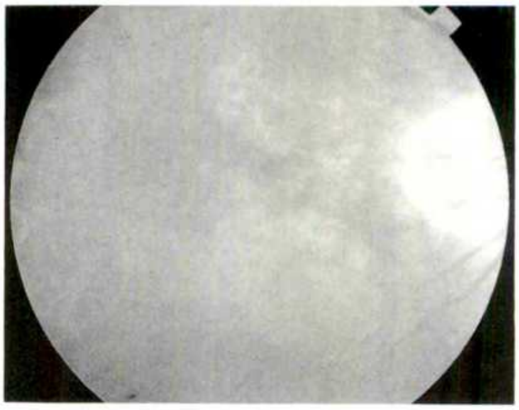

*Figure 1: One month after surgery.*

acuity (Table I). The fundal appearance of one month after surgery is shown in Fig 1.

Two of the patients had failure of treatment. Patient 1 had an aphakic type II detachment. He was treated as described and showed a partial response. The treatment was repeated twice but the detachment persisted. He then had a pars plana vitrectomy and gas tamponade procedure done. This was successful in reattaching his retina, with improvement in vision.

Patient 2 had a phakic type III detachment. She underwent the treatment as described. The retina was not completely attached after two weeks. However, she was reluctant to have the same procedure repeated. Instead she was successfully treated with a pars plana vitrectomy and gas tamponade, with improvement in vision.

In both these cases the presence of persistent posterior vitreoretinal adhesions was detected during vitrectomy. This was inferred by the tugging of the posterior retina during aspiration and cutting with the vitrectomy instrument round the area of the macular hole.

## Discussion

Macular hole retinal detachment is believed to be due to vitreoretinal traction on the macula.[9] After detachment has occurred the posterior vitreous face may be totally detached with no further traction, or there may be only a partial posterior vitreous detachment with persistent microscopic vitreoretinal adhesions. Such adhesions are often difficult to visualise, even with high magnification on slit-lamp biomicroscopy. However, their presence is often noted during vitrectomy, and the success of such an operation in relieving it further strengthens the case for such a cause.

The intravitreal gas possibly acts in two ways. (1) A bubble of sufficient size can rupture weak residual microscopic vitreoretinal adhesions, thereby relieving further traction.[14] (2) It seals the macular hole while the subretinal fluid is being absorbed.

In the case of patients 1 and 2 it would appear that the gas bubble was unsuccessful in breaking all the residual microscopic vitreoretinal adhesions.

This method of treating macular hole retinal detachment is simple, safe, and effective. The operative technique is straightforward and takes approximately 15 minutes to perform. It can be done under local anaesthesia. Operative equipment needed is minimal. The safety of the procedure has been noted in this and in Miyake's[12] series. There had been no operative complications and up to the present time; no occurrence of proliferative vitreoretinopathy has been documented. In this study it was also noted that failure of the technique did not worsen the prognosis when a pars plana vitrectomy had to be performed. A high success rate of 83% was obtained by Miyake using this technique. In the present series a lower but still highly satisfactory success rate of 71% was obtained.

Though the exclusion criteria would appear to restrict the number of cases that can be treated in this manner, in practice many of the patients can be selected for treatment. During the duration of this series eight patients with macular hole retinal detachments were seen. Of these only one had to be excluded, because of the presence of early proliferative vitreoretinopathy. Miyake was able to select 18 out of 24 patients with macular hole retinal detachments who were suitable for this method of treatment. It is likely that the proliferative potential in this condition is low, given that some patients have not been treated for at least three months without any evidence of retinal fibrosis.

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*British Journal of Ophthalmology*, 1990, **74**, 203–204

# Extracapsular cataract extraction under local anaesthesia without retrobulbar injection

R M Redmond, N L Dallas

## Abstract

**Day-case cataract surgery and the need for local anaesthesia are likely to increase. Retrobulbar (and peribulbar) anaesthetic injection is a common technique in cataract surgery, but serious complications are persistently reported. Subconjunctival injection is an alternative that avoids these risks. This retrospective study compares two groups of patients that underwent extracapsular cataract surgery under local anaesthetic. One group (retrobulbar) had uncomplicated retrobulbar injection with bupivicaine and hyaluronidase. The other group (non-retrobulbar) had superior bulbar, subconjunctival infiltration with bupivicaine and hyaluronidase. The operative complications and postoperative visual outcomes were similar in both groups. These results may encourage the investigation and adoption of the subconjunctival alternative to retrobulbar anaesthetic injection in cataract surgery.**

A recent editorial[1] advocated the use of subconjunctival infiltration in preference to retrobulbar injection for local anaesthesia in cataract extraction. The well recognised risks of retrobulbar injection include a 1% to 3% risk of retrobulbar haemorrhage,[2] perforation of the globe,[3] embolism of the central retinal artery,[2] and injection into the subarachnoid space.[4] Cardiac arrest, respiratory arrest, and seizures have been reported following retrobulbar injection.[5-7] This form of anaesthesia does not guarantee absolute ocular akinesia,[8] while the risks remain despite widely advocated changes in technique.[9] These risks can be avoided with subconjunctival infiltration. This alternative to retrobulbar injection was used for non-implantation, intracapsular surgery by individual surgeons in Glasgow over 20 years ago (Chisholm I A, personal communication). It is probable that the more recent introduction of hyaluronidase has improved its efficacy, and several registrars at the Bristol Eye Hospital have used non-retrobulbar local anaesthesia over the past five years. Nevertheless, the technique is not widely practised, and the suspicion remains that inadequate ocular akinesia results.

This retrospective report compares two groups of patients in whom extracapsular cataract surgery and lens implantation were performed under local anaesthesia. One group had retrobulbar anaesthesia, while the other did not. The patients were operated on by one registar only (RMR), and the distribution of types of anaesthesia used by the surgeon over the two-year period of the study is shown in Figure 1.

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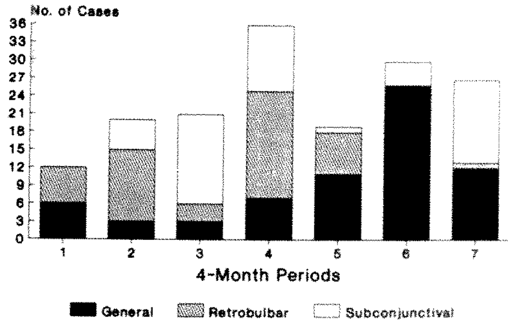

*Figure 1: Distribution of general, retrobulbar, and subconjunctival anaesthetic cases during the study period.*

## Patients and methods

Two groups, each of 50 Caucasian patients, are reported on. There were no significant differences in mean age (Table I) or male/female ratio between the two groups.

Patients in the retrobulbar group had topical benoxinate (Minims), an O'Brien facial block (supplemented when necessary with a van Lint procedure), and a retrobulbar injection (1·5–2 ml) through the lower lid with the eye in *downgaze* after puncture of the rectus cone. Patients in the non-retrobulbar group had a similar facial nerve and topical block. With the eye in downgaze and the upper lid retracted by the surgeon's thumb, a 23 gauge needle was used to infiltrate under the superior bulbar conjunctiva (approximately 1 ml), raising a bleb that extends from the superior limbus to beyond the insertion of the superior rectus tendon. 0·5% plain bupivicaine (Marcaine) with 1500 units of hyaluronidase was used for all injections.

Cases of retrobulbar haemorrhage which occurred in this two-year period have been excluded from this report and are not listed as complications in Table II. Far larger case series have already established the approximate risk of retrobulbar haemorrhage following injection.

Extracapsular cataract extraction under an operating microscope was standardised, with a

TABLE I *Mean age and age range of patients in retrobulbar and non-retrobulbar groups*

| | *Retrobulbar* *(n=50)* | *Non-retrobulbar* *(n=50)* |
|---|---|---|
| Age: | Mean=77·1 yr<br>Range=57–96 yr | Mean=76·1 yr<br>Range=62–94 yr |

TABLE II *Peroperative and early postoperative complications*

| | *Retrobulbar* *(n=50)* | | *Non-retrobulbar* *(n=50)* | |
|---|---|---|---|---|
| Astigmatism: | Mean=2·5 DC<br>Range=0·25–5 | | Mean=2·5 DC<br>Range=1–4·5 | |
| Complications (eyes): | Vitreous loss | 3 | Vitreous loss | 2 |
| | Iris prolapse | 1 | Residual cortex | 2 |
| | Wound leak | 2 | | |

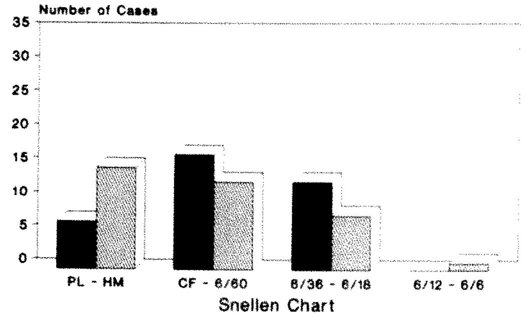

*Figure 2: Preoperative visual acuity in retrobulbar and subconjunctival cataract extraction cases.*

■ Retrobulbar

▨ Sub.conj. injection

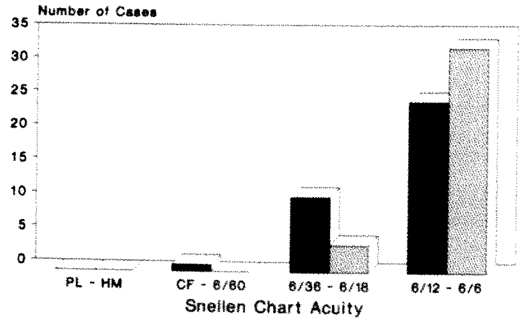

*Figure 3: Postoperative visual acuity in retrobulbar and subconjunctival cataract extraction cases.*

■ Retrobulbar

▨ Subconj. injection

superior rectus fixation suture, a fornix-based conjunctival flap, and a circular 'can opener' anterior capsulotomy performed in all cases. Lens nuclei were expressed rather than delivered with a Vectis and aspiration of residual cortex was either manual (McIntyre or Simcoe) or automated (Empac or Cavitron). In most cases the incision was closed with five interrupted stitches of 10/0 Prolene or nylon.

## Results

The final outcome was assessed in terms of improvement of visual acuity and the complication rate.

There was no difference in improvement of visual acuity between retrobulbar and non-retrobulbar groups, the mean improvement being from Snellen 6/60 to 6/9 (Figs 2, 3). Cases in which vision did not improve owing to previously unrecognised macular or optic nerve pathology have been excluded from the analysis of visual acuity. No significant difference was found in postoperative astigmatism between the two groups (retrobulbar, mean cyl=2·5 D; non-retrobulbar, mean cyl=2·5 D).

The frequency of peroperative and early postoperative complications for the two groups is shown in Table II. There were three cases of vitreous loss in the retrobulbar group and two in the non-retrobulbar group. All cases of vitreous loss occurred early in the two-year study period and were attributable to accidental rupture of the posterior capsule during cortex aspiration.

Scrutiny of the comments on operation sheets in all cases did not reveal a greater incidence of problematic ocular motility in the non-retrobulbar group. For three cases in this group there was a comment that the globe was convergent throughout the operation. Surprisingly, no patient in the non-retrobulbar group complained about the bright light of the operating microscope. In these cases it is unlikely that the optic nerve is 'blocked', especially early in the course of the operation.

The surgeon's subjective opinion was that retrobulbar injection tended to cause mo distress for the patient than subconjunctiv bupivicaine, and that peroperative anaesthes was adequate in both study groups.

## Discussion

General anaesthesia is regarded by most ophtha mic surgeons as being the ideal for extracapsul cataract extraction. Carbon dioxide monitori enables safe hyperventilation of the patient wi a relative collapse of the vitreous body an deepening of the posterior chamber. In additi ocular akinesia is assured. Local anaesthesia do not have these advantages. Nevertheless loc anaesthesia is widely used in the UK and occasionally requested by the patient. Day-ca surgery may become commoner in future, wi an attendant increase in local anaesthetic case

The complications of retrobulbar injecti have been listed above. It is conceivable that a intraconal retrobulbar injection might increa orbital tension and forward bulging of th vitreous, particularly if a small and undetecte intraconal haemorrhage occurs. Subconjunctiv infiltration will not have this effect. However, might be feared that greater rectus tone an greater ocular motility without retrobulb anaesthesia could heighten the risk of vitreou loss or of endothelial cell damage. These late fears were not borne out in this study.

Adequate ocular akinesia with only a subcon junctival injection of bupivicaine 0·5% an hyaluronidase is perhaps surprising. The anaes thetic rapidly diffuses to the superior rectus an the horizontal recti muscles. Intraconal diffusio is possible, but it is likely to be delayed and t represent only a small proportion of the origina volume of anaesthetic. The superior rectus bridle suture is an important factor in steadying the globe in the vertical plane, and the use of a 'one-handed' automated irrigation/aspiration system enables the edge of the section to be gripped with microforceps during cortex aspiration. Any residual movement is usually slight and in the horizontal plane, so that the surgeon can easily compensate for it.

This retrospective study supports the suggestion that consistently good results from extracapsular cataract extraction can be obtained without the use of retrobulbar anaesthesic injection.

We thank Mr P B Johnston for his advice and encouragement during the preparation of this paper.

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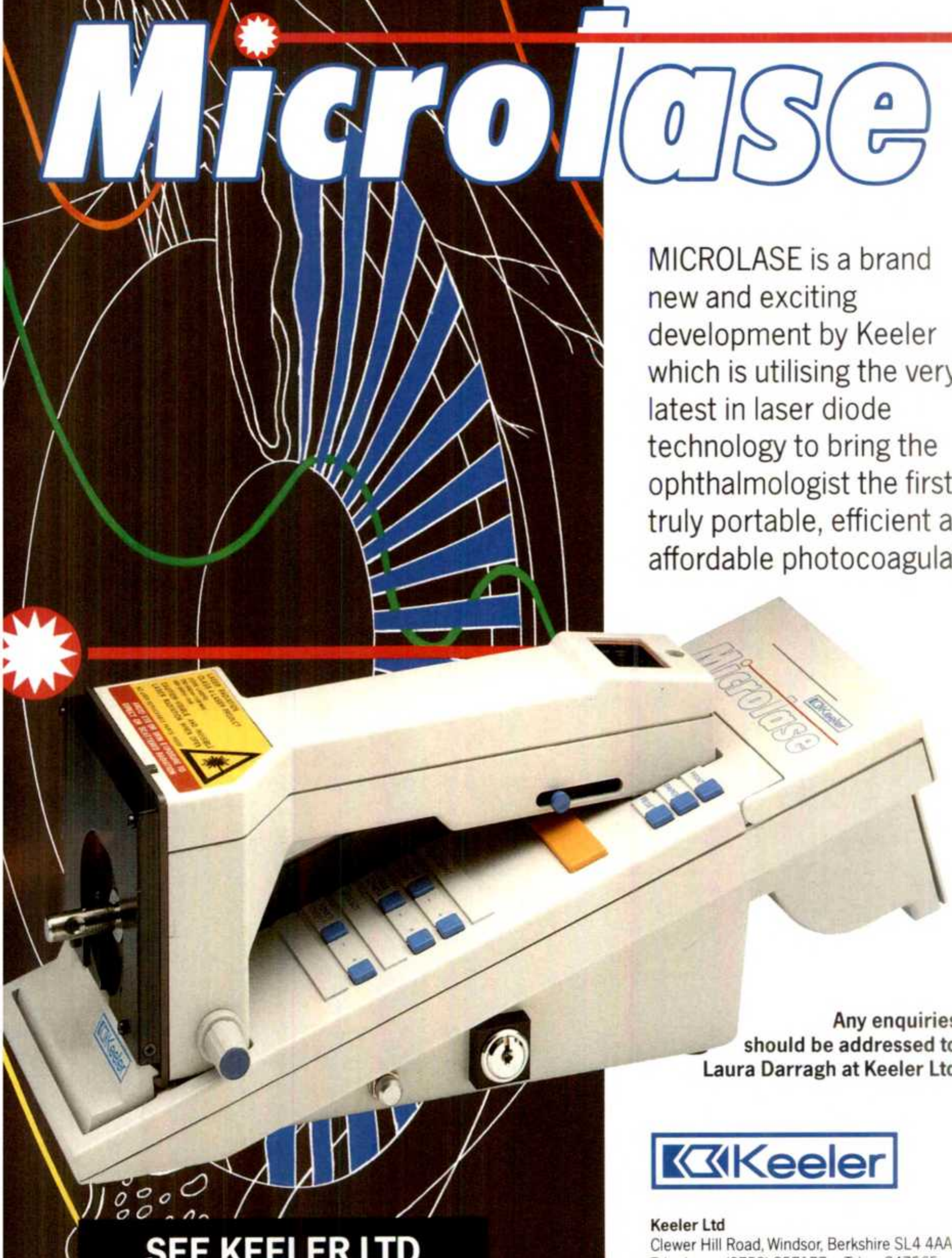

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*British Journal of Ophthalmology*, 1990, **74**, 205–207

# Cataract extraction without retrobulbar anaesthetic injection

Redmond Smith

**Abstract**

**Extracapsular cataract extraction with lens implant under local anaesthesia consisting of amethocaine drops followed by a simple subconjunctival injection in the upper part of the globe but without a retrobulbar injection was carried out in 175 eyes of 165 patients. The purpose of the study was to establish the feasibility of this type of anaesthesia in cataract surgery with the principal object of avoiding the possibility of retrobulbar haemorrhage and the other, rarer, complications of retrobulbar injection. The method, which is referred to as the NR method, proved to be satisfactory. No undue difficulties were encountered as a result of using the technique, the visual results were satisfactory and compared favourably with those under general anaesthesia, and the patients accepted the method well, possibly preferring it to conventional methods.**

Local anaesthesia for cataract has usually included a retrobulbar injection of a solution such as xylocaine or one of the longer acting anaesthetics. The reason for taking what to the casual observer seems a somewhat alarming step, namely, the plunging of a long and extremely sharp needle some 4 to 5 cm into the orbit in close proximity to the globe, has been the supposition that anything less would be likely to give less than adequate anaesthesia and akinesia. As has been pointed out recently, however, retrobulbar anaesthesia is not so essential a step as is widely believed.[1] Furthermore it is not without complications. Accidental perforation of the eye,[2] transitory blindness,[3] central retinal artery occlusion,[4] and cranial nerve palsy[5] have all been reported.

The present study arose out of a fortuitous occurrence. In March 1985 two successive cataract extractions had to be postponed owing to retrobulbar haemorrhage, and although, fortunately, no serious complications ensued, nevertheless the possibility of doing without the retrobulbar injection was considered. Simple peripheral iridectomy for angle closure glaucoma and fistulising operations of various sorts for open-angle glaucoma had always been performed without retrobulbar injection in the author's practice, but for the reasons mentioned above there had been no previous attempt to use the technique for cataract surgery. A trial of cataract extraction without retrobulbar anaesthesia was therefore started in April 1985 and continued until April 1988.

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## Material and methods

As time was relatively short owing to impending retirement it was decided to carry out a simple open trial of the technique, in effect a feasibility study rather than a comparative trial with formal controls. All patients listed for cataract extraction under local anaesthesia were (with a few exceptions to be mentioned later) operated on by the no retrobulbar (NR) technique. Approximately half of these were carried out at the Western Ophthalmic Hospital, London, and the remainder at a private clinic. All operations were performed by the author.

The total number of extractions during the period was 208 in 193 patients; 118 were female and 75 male. The mean age was 70·5 years (range 46–90, SD 14·5). The apparent infrequency of bilateral cases was due to two principal reasons. First, the operation on the other eye occurred outside the trial period; or, secondly, the other eye was operated upon by another surgeon in the clinical firm.

The total number of local anaesthetic (LA) operations in the series was 178, of which three were carried out by a retrobulbar and 175 by the NR technique. Thirty eyes were operated upon under general anaesthesia (GA). In one patient a general anaesthetic was used for the first eye and a local for the second. There were no patients in whom a local was used in the first eye and a general in the second. LA was used on both eyes of nine patients and GA on both eyes of four patients.

One patient operated on by the NR technique had simultaneous squint surgery.

### NR TECHNIQUE

The NR technique was carried out as follows. No premedication was used. Patients were reassured that little or no pain was likely to be felt. Some patients were afraid that they might prejudice the result of the operation by inadvertent movements but were reassured that this was in our experience extremely unlikely. Before towelling up the head two drops of amethocaine 1% were instilled into the eye, care being taken to apply the drops to the upper bulbar conjunctiva. Two or three minutes later a subconjunctival injection of up to 1 ml of 2% xylocaine was made in the upper bulbar region about 7 mm from the limbus. No attempt was made to enter the belly of the superior rectus muscle for fear of accidentally perforating the globe and the needle was always 'agitated' slightly from side to side to make certain that it was indeed in loose subconjunctival tissue only, before the injection was actually made. The bleb resulting from the injection was massaged downwards on the globe and could always be seen to extend to below the 3 and 9 o'clock positions on the limbus. In a few of the early cases separate injections were made over the medial and lateral recti, but this was found to be unnecessary and was therefore not persisted with. Facial block by O'Brien's technique was given up to June 1987 but was then discontinued. A Clark's speculum was used to hold the eye open during the surgery. This particular speculum, though it looks old fashioned, is extremely efficient and has two advantages over specula depending on a spring action to keep the eye open. First, the amount of opening is totally under the control of the surgeon, so that unduly forceful opening of the lids is avoided. Secondly, the speculum, once locked open at the separation chosen by the surgeon, is not subject to forced closure by the patient 'squeezing' – hence the reason for being able to dispense with facial block. The final manoeuvre before starting the extraction was the insertion of a superior rectus suture. Extraction was carried out by the extracapsular technique with a sequence of can-opener capsulotomy, simple expression, and cortical removal with a McIntire or similar canula. All the eyes had an intraocular lens implanted – a Sinskey type lens in most but a Severin in one and an unspecified lens in another. These were two eyes with vitreous loss. A third eye with vitreous loss could be seen to have only a limited hole in the posterior capsule and had a Sinskey lens with satisfactory results.

## Results

Results may be considered from three aspects: the visual results of the operations, the difficulties and complications encountered, and the patient's responses to the technique.

### VISUAL RESULTS

With such small numbers subtle differences from the expected norms would not be likely to show up, and, as mentioned in the introduction, this trial was no more than a feasibility study. However, purely for illustrative purposes, with no pretensions to statistical significance, the visual results of the three types of anaesthesia used during the period – NR, conventional retrobulbar, and GA – are displayed in Table I.

It can be seen from Table I that the visual results expressed as the visual acuities at approximately three months after operation appear reasonably satisfactory and there is no obvious difference between the NR and GA cases. Furthermore there is certainly no obvious difference between these results and what one has come to expect from local anaesthesia by conventional retrobulbar injection.

### DIFFICULTIES AND COMPLICATIONS

The expected difficulties due to excessive eye movements did not materialise. Moderate eye movements occurred in a few patients, but the impression gained was that the movements were no more troublesome than those which occur at times in retrobulbar cases, and there were no cases in which eye movements made any substantial difference to the ease with which the operation could be carried out. One patient made an alarming convulsive head movement during the operation, but this could have equally well happened during retrobulbar anaesthesia. Vitreous loss occurred in three eyes during NR. There was no vitreous loss in the GA cases. All the vitreous loss cases had a lens implanted, as mentioned previously, and the final visual acuities were 6/6, 6/9, and 6/9 respectively in the three eyes. Two other patients had had vitreous loss in their other eyes previous to the study while being operated upon under retrobulbar anaesthesia, one by me and one by a resident. The two patients whose retrobulbar haemorrhages in March 1985 had prompted the initiation of the study were eventually operated on during the study uneventfully by the NR technique.

TABLE I *Visual results of three types of anaesthesia*

| *Anaesthesia* | *Visual acuity* | | | | |
|---|---|---|---|---|---|
| | *6/5–6/6* | *6/9–6/18* | *6/24–6/60* | *Less than 6/60* | *No record* |
| NR | 54 (31%) | 101 (59%) | 9 (5%) | 8 (4·5%) | 3 (1·5%) |
| Retro | 1 – | 0 – | 1 – | 0 – | 1 – |
| GA | 10 (33%) | 16 (54%) | 3 (5%) | 1 (3%) | 0 – |

### PATIENTS' RESPONSES

Many patients were surprised at the painlessness of the procedure. The impression gained was that, owing to the preliminary conjunctival surface anaesthetic and the relatively shallow depth of the subconjunctival injection, the average patient actually did not feel any injection being given at all, and this effect was of course even more striking in those patients who did not have a facial block. Contrary again to what one had been led to expect (though in accord with experience during glaucoma surgery) those few patients who had an iridectomy rarely seemed to feel pain. Most patients, however, experienced some discomfort during the insertion of the conjunctival sutures into the upper lip of the wound at the conclusion of the operation. But in my experience this is exactly the same as what happens after retrobulbar anaesthesia, though it may be better after a long-acting type of local anaesthetic, material with which I have had no personal experience.

Only one patient experienced severe pain during the operation, and it has to be admitted that this was a distinctly unnerving experience. The patient was a very obese West Indian female on whom the local anaesthetic seemed to be almost ineffective. As she was adamantly opposed to GA, the second eye was operated on with a retrobulbar anaesthetic, and I was surprised to find that this proved to be even worse than the NR operation. Fortunately both procedures were carried out satisfactorily, but it seemed clear that in this particular patient it was not the NR technique which had caused her pain in the first operation but a resistance to the anaesthetic material itself.

None of the patients operated on by the NR technique requested a different technique for the second eye.

## Discussion

One of the most obvious differences between surgeons and even institutions is the large variations that occur in the ratio between numbers of cataracts done under LA and under GA. It is unlikely that the populations being operated on differ substantially from one another, especially within one country, so that the indications for LA or GA must depend more on the personal preferences of the surgeons than the medical condition of the patients. One is told repeatedly that old and infirm patients are just as safe under GA as LA, but I have to confess that I personally doubt whether this is always true. Furthermore, from a purely financial point of view, if extensive day-case surgery is going to become more widely practised, skill and confidence in local anaesthesia need to be improved. I have the distinct impression that there are some surgeons, of the highest skill in many cases, who are distinctly uncomfortable with local anaesthesia. This probably accounts for the high GA/LA ratio in some centres. The difference between conventional retrobulbar LA and the NR technique is not great; it is in fact a difference of detail only. Surgeons will have to judge for themselves whether the fact that the NR technique appears to be, if anything, pleasanter for patients than retrobulbar anaesthesia, and that it avoids the possibility of retrobulbar haemorrhage, not to mention the other admittedly rare complications, is sufficient reason for their abandoning retrobulbar anaesthesia and trying the NR technique.

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# Indirect choroidal ruptures: aetiological factors, patterns of ocular damage, and final visual outcome

Christopher Mark Wood, John Richardson

## Abstract

**Indirect choroidal ruptures result from blunt ocular trauma and have a pathognomonic fundal appearance. We analysed a group of 30 patients with indirect choroidal ruptures with specific reference to the circumstances of the injury, the pattern of ocular damage, the cause of any visual loss, and the final visual outcome. Using this analysis we deduce a pathogenetic explanation for the characteristic fundus signs in patients with indirect choroidal ruptures. The majority of cases were young males injured during sport or by an assault, a minority were injured at work. Diffuse non-focal impact injuries due to punches were associated with ruptures concentric with and adjacent to the optic disc. Focal impact injuries, due to projectiles, showed more extensive ocular damage. Seventeen of 30 patients regained 6/12 vision after injury. Injuries due to projectiles and temporally situated ruptures were associated with a poorer visual outcome than others. Macular damage was the commonest cause of visual loss, principally due to pigmentary maculopathy, traumatic inner retinal damage, and choroidal neovascular membranes rather than direct foval damage by the rupture.**

The typical appearance in the fundus of indirect choroidal ruptures is well documented.[1-3] Little attempt has been made to explain the mechanism by which peripapillary ocular damage results from closed trauma to the anterior segment or to relate the clinical appearance of indirect choroidal ruptures with the type of injury sustained and the final visual outcome.

We report here our studies on a group of patients with indirect choroidal ruptures, noting the circumstances of the injury, the extent of ocular damage, cause of any visual loss, and long-term visual outcome. We suggest a working hypothesis to account for the mechanism of production of indirect choroidal ruptures and pose the question of a possible role of minor trauma in presumed non-traumatic maculopathies.

## Materials and method

At total of 30 patients with indirect choroidal ruptures following blunt ocular trauma were studied (27 males and three females). The patients were either followed up prospectively from the time of the injury (seven cases) or were already being followed up (16 cases), or they were identified as having an indirect choroidal rupture from our photographic files and asked to attend for further examination (seven cases). The average age at the time of the injury was 24 years (range 8–45 years). The average follow-up time after injury was 4½ years (range 6 months to 41 years, though in only two cases had the injury occurred more than 10 years previously).

All the patients gave a detailed history of the original injury and then had a full ophthalmic assessment – including computerised visual fields, retinal photography, fluorescein angiography, electroretinography, and measurement of pattern reversal visual evoked potentials.

Individual fundal photographs were projected on to a screen, enabling the outlines of each rupture to be marked. By this method composite patterns of rupture following different types of injury were produced. For ease of comparison all slides were projected to produce the image of a left fundus – that is, photographs of right fundal lesions were inverted.

## Results

From the patients' histories we could identify three groups of circumstances in which the injury occurred – namely, sport, assaults, and accidents at work. Eight of 11 injuries due to sport occurred in males aged 11–15 years, and in 9/11 cases the left eye was injured ($0{\cdot}05>p>0{\cdot}02$). Nine of 13 of the injuries following assaults occurred in males aged 15–31 years; in 8/13 cases the left eye was injured (not a significant difference). Accidents at work accounted for six cases, four of these patients being over 30 years old; in 2/6 cases the left eye was affected (not a significant difference).

The type of injury was divisible into two groups – those due to punches, where the eye was subjected to a diffuse force, and those due to projectiles, which had a more focal impact on the globe. The distribution of ruptures in seven eyes subjected to punches is shown in Figure 1 and can be seen to be mainly restricted to the peripapillary region. These ruptures were

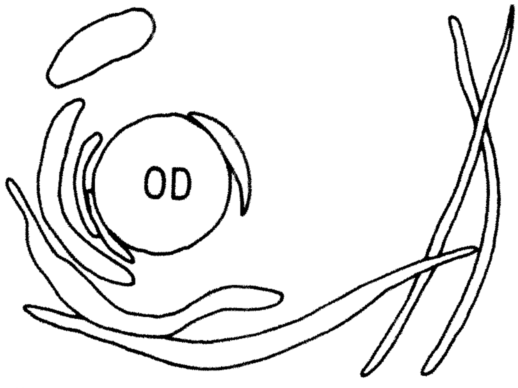

*Figure 1: Composite diagram illustrating the sites of indirect choroidal rupture in eyes suffering injuries due to punches.*

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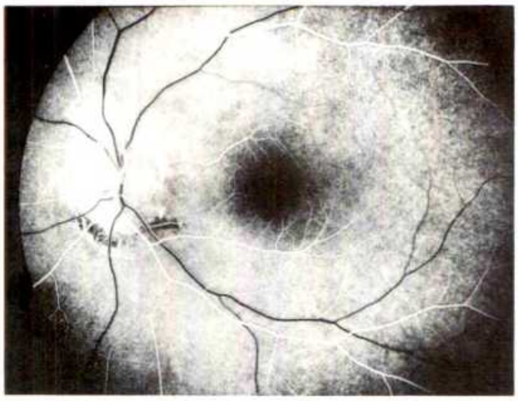

*Figure 2: Indirect choroidal rupture inferior to the disc following a punch. Fluorescein angiogram shows a partial thickness rupture with smooth curved appearance.*

typically curved or curvilinear in appearance, concentric with, and usually inferiorly or temporally to, the disc (Fig 2). Anterior uveal injuries were minimal, with only one case of significant angle recession and no cases of direct choroidal ruptures (Table I).

Indirect choroidal ruptures resulting from injuries due to various projectiles, hand held implements, or kicks (Table II) striking the eye are shown in Figure 3. These indirect choroidal ruptures were less likely to occur near the disc (Fig 4) and more likely to be multiple, extensive, and irregular. The associated anterior uveal injuries were also more severe (Table I), sometimes indicating the site of impact. Five patients had a continuous path of damage extending from the anterior uvea as a direct choroidal rupture or iridodialysis, through areas of retinal pigment epithelium damage, to indirect choroidal ruptures at the posterior pole. This more extensive pattern of ocular damage reflects the more severe nature of the injury due to the higher kinetic energy and focal impact on the globe.

The majority of patients (17/30) regained vision of 6/12 after the injury. Temporally situated ruptures were associated with a poorer visual outcome (Table III), as macular damage was more likely to occur. In five eyes ruptures involving the fovea appeared to be directly responsible for a reduction in vision. However, in a further 10 eyes with macular damage the rupture did not directly involve the fovea, and a pigmentary maculopathy (eight eyes) or inner retinal damage (two eyes) were responsible for the loss of vision. There were two cases where a thin partial thickness rupture passed very close to the fovea (Fig 5), yet the patients retained good central vision. Patients suffering an injury as a result of a punch retained a better level of visual acuity than patients suffering an injury due to a projectile (Table IV).

TABLE I *Characteristics of indirect choroidal ruptures related to type of injury sustained. Included in the projectile group are kicks and hand held weapons such as pickaxe handles*

| | | *Punches (n=7)* | *Projectiles (n=23)* | *Overall (n=30)* |
|---|---|---|---|---|
| Site | Peripapillary | 7 | 13 | 20 |
| | Peripheral | 0 | 10 | 10 |
| Number | Single | 4 | 9 | 13 |
| | Multiple | 3 | 14 | 17 |
| Appearance | Curved | 7 | 17 | 24 |
| | Irregular | 0 | 6 | 6 |
| Anterior uveal injury | | 1 | 16 | 17 |

TABLE II *Types of projectiles or weapons responsible for focal impact injuries to the eye*

| | |
|---|---|
| Arrow/stick | 8 |
| Metal | 5 |
| Stones/brick | 4 |
| Plastic | 2 |
| Squash ball | 2 |
| Kick | 2 |

Visual field defects noted corresponded to areas of retinal pigment epithelium damage visible ophthalmoscopically rather than to the individual ruptures, and there were no nerve fibre bundle scotomata related specifically to an indirect choroidal rupture. There were three patients with nerve fibre bundle field defects which did not correspond to the chorioretinal injury and one patient with an altitudinal field defect. In these four cases we considered that the clinical appearance of the optic disc (haemorrhage on the disc in the acute stage, or pallor out of proportion with the fundal changes) and the field defect together with abnormal visually evoked responses suggested the presence of a primary optic nerve injury in addition to the chorioretinal damage.

Electrophysiological assessment generally reflected the fundal changes, patients with extensive retinal pigment epithelium changes having abnormal electroretinograms. As the macular region dominates the pattern visually evoked potential (VEP), delay in the response or a reduction in amplitude was seen in patients with overt macular damage. Two patients with apparently healthy maculae had VEPs with delay or reduced amplitude due to the presence of an optic nerve injury. A further two patients with extensive field defects and optic atrophy as well as macular damage had grossly abnormal VEPs due to the combination of macular and optic nerve injuries.

Delayed complications may occur after concussional eye injuries,[2-4] leading to further (or late) visual loss, and 8/30 of our series developed changes which could have led to a further deterioration in visual function (one patient with glaucoma, two with retinal detachments, five developing subretinal neovascular membranes).

## Discussion

Eye injuries most commonly affect young males and represent a significant cause of visual loss.[5 6] Concussional injuries result from the direct effect of trauma at the site of impact or from the effect of transmitted force.[4] Energy can be transmitted across the globe either through the vitreous gel (contrecoup theory)[7] or via the walls of the globe.[8] However, the contrecoup theory cannot account for the path of damage from impact site to posterior pole which we observed in some of our patients. In addition, since the eye is most vulnerable to injury from an inferotemporal direction,[9] then injuring forces passing directly through the vitreous (as in the contrecoup theory) could be expected to produce choroidal ruptures on the nasal side of the disc, whereas in fact most are located on the temporal side. Experimental work on pigs' eyes suggests that the transmission of energy in concussional eye injuries occurs via the walls of the globe[8] and has been unable to demonstrate evidence of contrecoup injury.[10] To our knowledge no experimental study has been able to demonstrate convincingly the existence of contrecoup forces in the pathogenesis of concussional eye injuries. Thus the contrecoup mechanism may explain

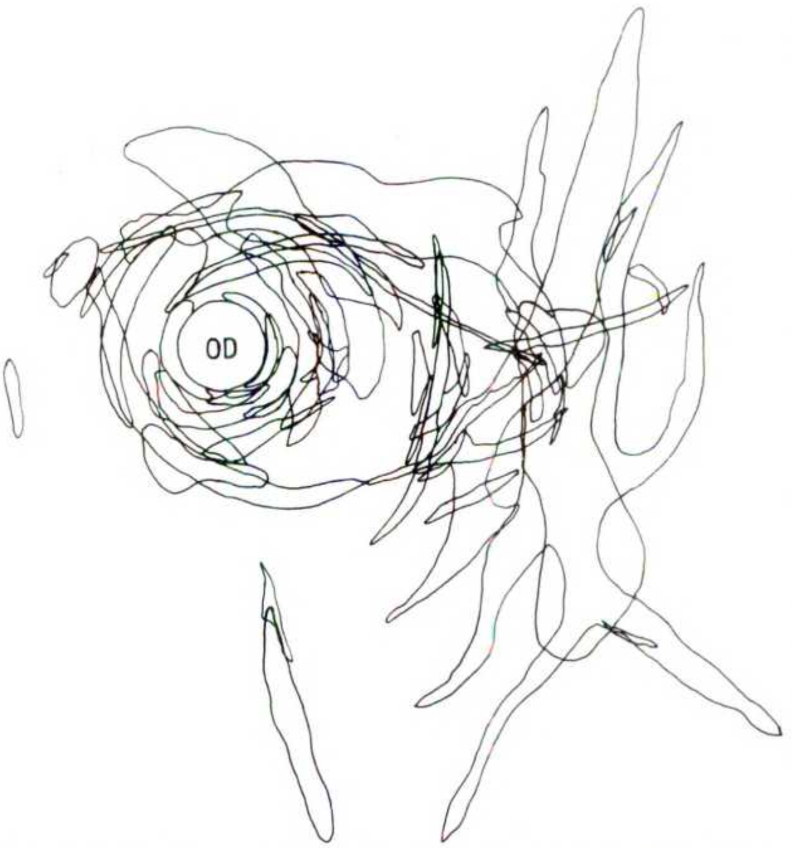

*Figure 3: Composite diagram illustrating the sites of indirect choroidal ruptures in eyes suffering injuries from projectiles, various weapons, and kicks.*

TABLE III *The final visual acuity related to the site of the choroidal rupture*

| | *Temporal (n=13)* | *Nasal (n=4)* | *Inferior (n=8)* | *Superior (n=5)* |
|---|---|---|---|---|
| 6/5–6/12 | 5 | 4 | 6 | 2 |
| 6/18–6/60 | 3 | – | 2 | 1 |
| <6/60 | 5 | – | – | 2 |

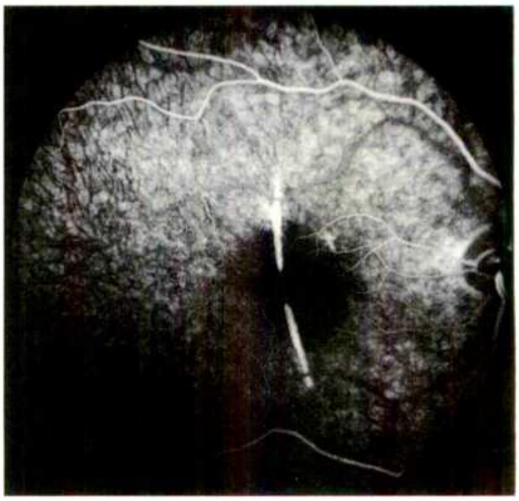

*Figure 5: Fluorescein angiogram of a smooth curved rupture through the perifoveal area in an eye regaining 6/5 vision after the injury, though late visual loss occurred due to a disciform maculopathy.*

damage to movable structures within a rigid sphere such as the skull but does not account for the pattern of damage in a resilient, deformable sphere such as the globe.

When energy is conducted through the walls of a sphere, any point at which there is a discontinuity in the wall, or an attachment to the wall, will cause a localised increase in stress. Consequently the attachments at the vitreous base will produce localised increase in stress in the peripheral retina. Similarly the discontinuity produced in the wall of the globe by the entry of the optic nerve and posterior ciliary arteries, together with the effect of external attachments to the wall of the globe (the optic nerve, posterior ciliary vessels and the inferior oblique, and the internal attachment of the posterior vitreous) will induce an increase in stress in the peripapillary retina and choroid.[11] The overall effect is that acute deformation maximises stress at the peripheral retina and the peripapillary retina and choroid, leading to ruptures or tears at these sites. This predicted pattern of damage is in keeping with our clinical findings.

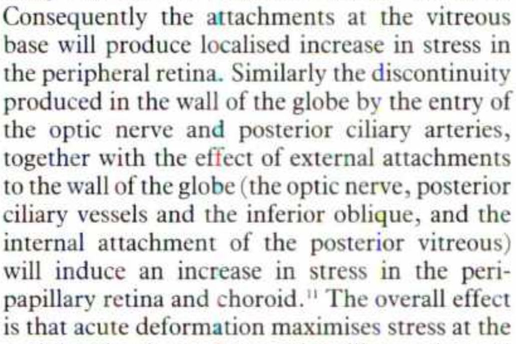

*Figure 4: Fundal photograph of indirect choroidal ruptures following severe ocular trauma due to repeated kicks in the face during an assault.*

Punch injuries have a diffuse impact on the globe, owing to the protective effect of the orbital margin, and the ruptures are exclusively peripapillary. This represents damage occurring only at the most vulnerable site, whereas injuries due to a projectile which has a focal, unimpeded impact on the globe result in more widespread ocular damage due to the higher energy imparted. The great majority of indirect choroidal ruptures occur temporally or inferiorly to the disc, reflecting vulnerability of the eye to injury from the inferotemporal direction[9] rather than localised differences in Bruch's membrane or the choroid.

## CONCLUSIONS

(1) Severe concussional eye injuries occur predominantly in young males. Of particular note is the finding that such injuries in teenagers are most likely to occur as a result of sports injuries, and this conclusion has been confirmed by a recent survey of ocular injuries.[12]

(2) Indirect choroidal ruptures occurring temporal to the disc are much more likely to be associated with visual loss than those occurring nasally, owing to the increased risk of macular damage from the direct effect of the rupture,

TABLE IV *Final visual acuity according to the type of injury: punches (diffuse impact on the globe), or projectile/weapon (focal impact on the globe)*

| | *Punches (n=7)* | *Projectiles (n=23)* | *Overall (n=30)* |
|---|---|---|---|
| 6/5–6/12 | 5 | 12 | 17 |
| 6/18–6/60 | 1 | 5 | 6 |
| <6/60 | 1 | 6 | 7 |

inner retinal damage, pigmentary retinopathy, or the late development of a subretinal neovascular membrane.

(3) Peripapillary choroidal ruptures occurring in the presence of minimal anterior segment injury imply an injuring force of diffuse impact or only moderate severity. Consequently, provided the macula has not been severely damaged, the patient has a relatively good visual prognosis.

Extensive multiple ruptures which are irregular and associated with significant anterior segment damage imply that the globe has been subjected to severe deforming forces, probably of focal impact. Ocular damage is more widespread, macular and optic nerve injury more likely, with a poorer visual prognosis.

(4) Indirect choroidal ruptures are due to the generation of maximal stress at the peripapillary area in closed ocular injuries, probably mainly owing to forces generated in the wall of a gel-containing flexible compressible sphere with external and internal fixed attachments. The peripapillary region is thus vulnerable to closed ocular trauma, and it is feasible that subclinical peripapillary ocular damage may result from repeated minor ocular trauma. The latter may play a part in the onset of maculopathies of presumed non-traumatic character.

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# A computerised diagnostic index for medical and neuro-ophthalmology

W H Woon, D J Spalton

**Abstract**

**We have developed a classification that meets the requirements of the Medical Eye Unit and computerised it. The classification uses three categories: anatomical site of lesion, pathological process, and clinical diagnosis. Each patient is identified by standard data and up to three entries in each of anatomical localisation, pathological diagnosis, and clinical diagnosis. This system allows the formation of groups of patients which can be either very specific or very broad by appropriate combination of selection criteria in the different categories. No codes are used but computer validation ensures consistent nomenclature. Computerisation allows rapid searching of records even with multiple selection criteria. The program is simple to use and validates data entries. An additional benefit is that it facilitates medical audit of the department's work.**

Computerised data bases greatly facilitate the retrieval and correlation of information.[1] However, their usage and practicability very much depend on having a satisfactory classification system of data entry as well as a computer system that is user friendly.

Problems of classification are a particular problem in medical and neuro-ophthalmology, where patients may have rare and esoteric diagnoses or several diseases. A simple listing of clinical diagnoses is inadequate, as patients may have multiple diagnoses – for example, a patient with cryptococcal meningitis, raised intracranial pressure, and occipital cortical infarct – or a diagnosis may be described in several ways – for example, diabetic third nerve palsy, microvascular third nerve palsy, pupil sparing third nerve palsy – or a firm diagnosis may be difficult to establish with certainty. An additional problem with a simple listing of clinical diagnoses is that it is difficult to compile retrospective series of diagnostic, anatomical, or pathological entities such as all third nerve palsies, a review of all orbital disease, or all cases of genetically associated optic atrophy.

There have been modifications of the International Classification of Disease Code (ICD)[2] for ophthalmic use, and these have been computerised. An example of such a code is the Wilmer Information System (WIS).[3,4] The WIS code is designed to identify patients by diagnosis or procedure, and to allow extension for further subclassification. However, the structure of the ICD does not meet our requirements. The hierarchial structure of the ICD and its classification mainly along anatomical lines allows easy formation of broader anatomical groups. The code does not allow easy arrangement of patients into different groups – for example, groups classified according to pathological process rather than anatomical site of lesion. We have decided to classify patients by three categories: anatomical site of lesion, pathological process, and clinical diagnosis. We have also decided to avoid a code system altogether, as relational databases allow checking of the diagnoses entered to make sure that they agree with a standard nomenclature. In essence the standard nomenclature has become the code. This system means more typing for the user but saves the user looking up a code, and it is probably less intimidating to the infrequent user.

A classification system using more than one means of classification needs to be computerised, as selecting outpatients on a combination of selection criteria would be very arduous by hand. Problems of computerisation are that the system must be accessible to people who may be with the department for only a short period and who may have no prior knowledge of computers or the classification system used. The system must ensure that data are entered in a consistent manner, otherwise data retrieval will be incomplete. This can be achieved by having files of appropriate entries against which the computer can check data input.

## Classification

Standard data on all patients are entered for personal identification. Patients are then classified by anatomical localisation, pathological diagnosis, and clinical diagnosis. In each of these three classes three listings are possible to allow for multiple diagnoses. Table I shows the data that may be entered for each patient. For the use of the medical eye department the alternatives for anatomical localisation and pathological

TABLE I: *Data which may be entered for each patient*

| Name | Hosp No | Age | Sex | Consultant | Date of Admission | District |
|---|---|---|---|---|---|---|
| | | | | | | |

| Anat Localisation | Path Diagnosis | Clinical Diagnosis |
|---|---|---|
| | | |
| | | |
| | | |

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TABLE II *The allowed entries for anatomical localisation and pathological diagnosis*

| *Anatomical localisation* | *Pathological diagnoses* |
|---|---|
| Cutaneous (eyelids, etc.) | Degenerative |
| Ocular | Demyelination |
| Optic disc | Dystrophy |
| Optic nerve | Genetic |
| Chiasm | Infection |
| Optic tract | Inflammatory |
| Cortical | Raised intracranial pressure |
| Orbit | Trauma |
| Ocular motility | Tumour |
| | Vascular |

diagnosis are purposely limited to force choice. Table II shows the allowed entries for anatomical localisation and pathological diagnosis. The list of clinical diagnoses may be easily extended at the time of data entry if the list contains no appropriate diagnosis.

Patients are classified according to a combination of broad categories (anatomical localisation and pathological diagnoses) and specific categories (clinical diagnoses). Combining selection criteria for these categories allows the formation of many more categories. For instance, selection criteria in anatomy and pathology could be combined to pick out all patients with ocular motility problems due to demyelination (all cases of multiple sclerosis with ocular motility defects). Another example would be to combine selection criteria in anatomical localisation and clinical diagnosis to pick out patients with sarcoid who have an optic nerve lesion. Combining selection criteria in all three classification groups could be used to pick out patients with ocular inflammation due to sarcoid.

Judicious use of combinations of selection criteria can be used to find patients who may have been misclassified or who may be hidden away in a very specific diagnosis which does not come readily to mind. For instance, data on all patients with heredofamilial optic atrophy, whatever their precise clinical diagnosis, could be retrieved by selecting optic nerve for anatomical localisation and genetic for pathological diagnosis.

## Method

A user friendly program was written with the dbase III plus package[5 6] for a conventional IBM compatible computer with a 20-megabyte hard disc. The system created is entirely menu driven, having instructions, on screen, on how to proceed at every stage. There is no need for the user to resort to either the dbase III assist menu or have any knowledge of the dbase III language.

Consistency of data input is vital for correct data retrieval, and the program incorporates extensive validation of data input. The picture function[6] and picture template option[6] are used to restrict entries to upper case letters and to provide punctuation for initials. For entries other than names and hospital numbers the computer accepts only entries that match with stored acceptable lists. If the computer rejects an entry, the user is presented with a list of acceptable entries. Extension of these lists of acceptable entries can be done at the time of patient data entry for the clinical diagnosis. Extension of the lists of anatomical localisation and pathological diagnoses is made more difficult in order to keep these two lists small, forcing choice and preventing duplication.

An opening menu provides the user with the options which include adding new patient records, editing previous patient records, searching the patient database file, and copying the database files on to a floppy disc. A customised and more friendly screen has been produced for data entry using the modify screen[6] command. The program uses 11 public variables[6] corresponding to each field in the patient's record database file. Data are entered into these public variables, and validation is performed, before they are entered into the patient's record database. This system means that the delete[6] and pack[6] commands are not used in the program and removes the hazard of an inexperienced user aborting the program in the middle of a pack command, when all data may be lost.[7] The comparison operator,[6] is used to validate the entries, for sex and district, for which only a few entries are allowed. For entries for consultants, anatomical site of lesion, pathological process, and clinical diagnosis four database files[6] are used to store lists of acceptable entries. Validation of data entry is then performed by matching with values in the appropriate database files.

The database files for allowed values of anatomy, pathology, and diagnosis are indexed[6] to allow faster searching of them with the find[6] command rather than the slower locate[6] command. The user can search the patient record database for a given name or hospital number. He can also select outpatient records by entering selection criteria for lower and upper age limits, limits for date of admission, sex, district, consultant, anatomy, pathology, and diagnosis. Values entered into this combination of selection criteria then provide a filter for selecting outpatient records. If a selection criterion is left blank, then no selection is made on that field.

The selection criteria are joined by the 'and' relation.[6] To prevent the user escaping to the dot prompt, on escape[6] and on error[6] are used to place the user with the opening menu. This is done in preference to using set escape off,[6] as there may be occasions when the user wants to escape from a particular part of the program.

In theory an error will never be invoked by the program, as the program should be able to deal with all possible errors by the user. The user is encouraged to copy the database files on to a floppy disc in case the data are lost from the hard disc. Each patient record requires 306 bytes of memory.

## Discussion

The program that has been developed is now in operation with the Medical Eye Unit at St Thomas's Hospital. It produces a very full description of every case, and it has proved to be user friendly. Data entry is simple and data validation has been effective. Searching of the data base has been rapid, specific, and complete.

We should welcome the development of similar data bases in other centres, so that exchange of records between centres could be easily achieved, which would allow access to many more patient records. A compatible national data base would allow interested clinicians to compile large lists of patients and aggregate rare cases for future research.

To this end we should be happy to supply the program written to other users. The user would require an IBM compatible machine and for copyright reasons must be in possession of the dbase III program. The user must register under the Data Protection Act, which is simply done with the appropriate hospital administrators.

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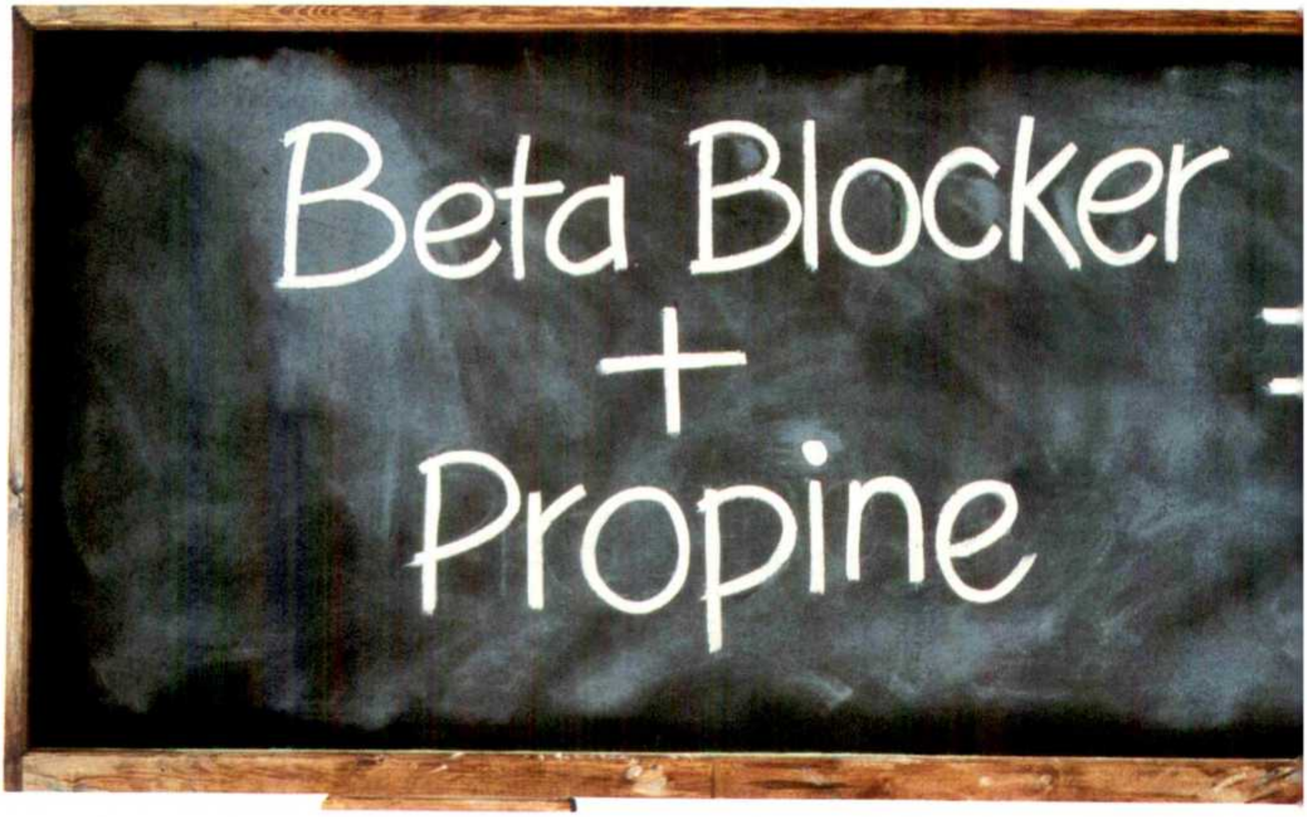

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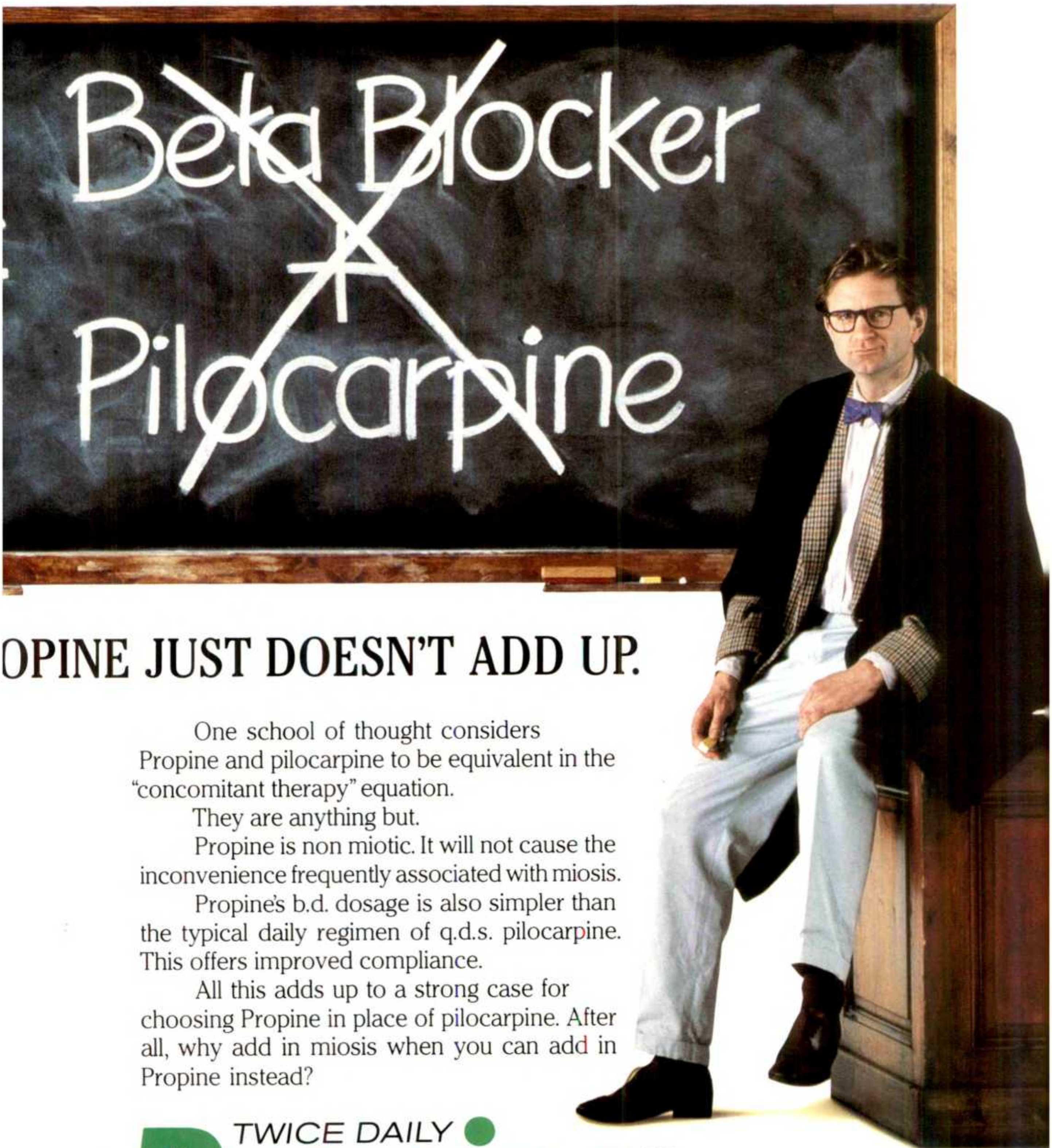

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*British Journal of Ophthalmology*, 1990, **74**, 215–219

# Brightness discrimination and contrast sensitivity in chronic glaucoma – a clinical study

Su Lin Teoh, Donald Allan, Gordon N Dutton, Wallace S Foulds

**Abstract**

**The visual acuity, the difference in sensitivity of the two eyes to light (brightness ratio), and contrast sensitivity were assessed in 28 patients with chronic open angle glaucoma and compared with those of 41 normal controls of similar ages and visual acuity. The results obtained were related to the results of Tübingen visual field analysis in patients with glaucoma. Twenty-four of the 28 glaucoma patients (86%) had a significant disparity in brightness ratio between the two eyes. This was found to match the frequency of visual field loss. Moreover, there was a significant relationship between the interocular differences in brightness sense and the difference in the degree of visual field loss between the two eyes. Of the glaucoma patients 39% had sum contrast sensitivities outside the normal range for age-matched normal controls. No significant correlation was found between the interocular difference in brightness sense and the visual acuity or the interocular difference in sum contrast sensitivity. It is concluded that, in the presence of a normal visual acuity, the brightness ratio test warrants evaluation as a potential screening test for chronic open angle glaucoma.**

The diagnostic features of primary open angle glaucoma comprise raised intraocular pressure and cupping of the optic disc in association with characteristic visual field defects.[1] Other methods of clinical evaluation include contrast sensitivity[2,3] and retinal nerve fibre layer photography with red-free light.[4] It has been suggested that contrast sensitivity, measured by Arden gratings, may provide a sensitive means of evaluating patients with open angle glaucoma.[2] Subsequent studies have failed to validate this finding.[5,6] However, with the use of electronic testing systems with a wide range of spatial frequencies abnormalities of contrast sensitivity have been shown.[7] Photography of the nerve fibre layer of the retina requires considerable skill both to take and to interpret,[4] which limits the use of this method.

Apparent reduction in the brightness of objects or the intensity of colour is a well recognised feature of optic nerve disease. The difference in the perception of colour brightness between the two eyes is commonly used clinically to evaluate optic nerve function.[8] A quantitative means of assessing brightness discrimination has been described.[9] Crossed polarising lenses are placed in front of each eye, and the angle between the pair in front of the better eye is altered until light is perceived as having equal intensity for each eye.[10]

The purpose of the present study is to determine whether the interocular difference in brightness sense is abnormal in patients with primary open angle glaucoma. The results obtained have been analysed with regard to sensitivity and specificity for the detection of glaucoma and compared with those of visual acuity, visual field, and contrast sensitivity.

## Materials and methods

### PATIENTS AND CONTROLS

Twenty-eight patients with chronic open angle glaucoma were examined. Twenty-four had bilateral glaucoma and four unilateral. Eighteen were male and 10 female. Ages ranged from 31 to 81 years (mean 64 years). All had visual acuities of 6/9 or better except for eight patients with visual acuities between 6/12 and 6/36 due to lens opacities. They all fulfilled two or more of the following criteria for the diagnosis of glaucoma:

(*a*) An intraocular pressure equal to or greater than 21 mmHg on two or more occasions.

(*b*) Visual field loss. Nerve fibre bundle defects represent early glaucomatous field loss, and these manifest as circumscribed paracentral defects, nasal steps, arcuate scotomas, and sector shaped defects. Progression of field loss may produce an increase in the density of existing scotomas, new scotomas, and ring scotomas. In advanced glaucomatous field loss, a tunnel vision or a temporal island of vision may be all that is left.

(*c*) Pathological cupping of the optic disc with characteristic changes at the neuroretinal rim.[1,11,12]

Patients who had additional ophthalmic pathology and patients with anisocoria greater than 2 mm were excluded from the study.

Forty-one normal subjects (81 eyes) with ages ranging between 13 and 70 years (mean 38 years) were examined as controls. Twelve were male and 29 female. The visual acuity in all eyes was 6/9 or better. In all cases a detailed medical history was taken.

### CLINICAL METHODS

Detailed clinical ophthalmic examination was carried out on all patients and controls. The best corrected visual acuities for near and distance were determined. The pupil diameters were compared in room luminance comparable to the background luminance used for the brightness discrimination test.

A single observer performed central Tübingen visual field assessment on all glaucoma patients using at least two isoptres. Each visual field loss was scored according to the protocol described by Thompson and colleagues[13] but modified by

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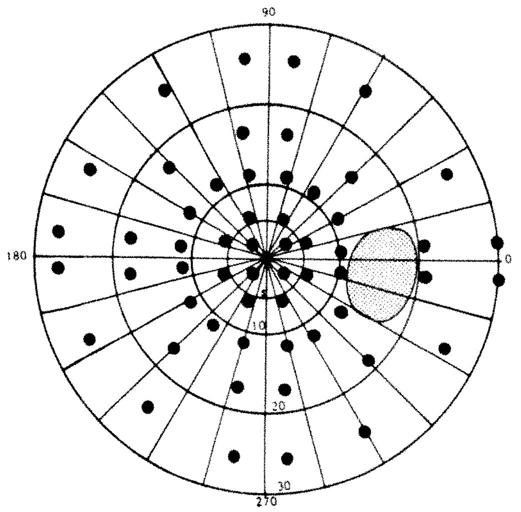

*Figure 1: Visual field score. This is a diagram of the central Tübingen field chart. Each visual field defect was scored according to a protocol modified from that of Thompson* et al[13] *where solid points were marked at regular intervals within the central 30° of visual field. Any solid point falling within areas of relative scotoma, with 10 apostilb target, was given a score of 0·5, and any point within areas of scotoma to 0·5 apostilb target was given a score of 1. For points falling within areas of absolute scotoma a score of 2 was given to each point.*

giving extra weighting to the score according to the density of the scotoma (Fig 1). Figure 1 is a diagram of the central Tübingen field chart where solid points are marked at regular intervals. Any solid point falling within areas of relative scotoma, with 10 apostilb target, was given a score of 0·5, and any point within areas of scotoma to 0·5 apostilb target was given a score of 1. For solid points falling within areas of absolute scotoma a score of 2 was given to each point. The visual field loss was then scored by adding all the scores of all points present on or within all scotomata in the visual field. Therefore visual field loss had a score range of 0 (no scotoma) to 114 (absolute scotoma in the whole central 30° of field).

The brightness comparison test was carried out with a standard trial frame with a pair of polarising lenses on each side.[9] The rear lens was fixed and the front lens was rotated to alter the amount of light transmitted. (A calibration curve giving the percentage of light transmitted as a function of angular difference between polarisers had been determined in an initial experiment.) Each subject was seated at 1 metre from an *x* ray viewing box which emitted a homogeneous white light with a luminance of 640 lumina m$^{-2}$. The box subtended 70° of visual field horizontally and 40° vertically. The lenses were first set for maximum light transmission. Each eye was alternatively covered and the subject asked to comment on any disparity in brightness between the two eyes. The front polarising lens of the 'better eye' was then rotated to decrease the amount of light transmitted till its brightness appeared equal to that in the 'worse eye,' in which light was 100% transmitted. (The pair of polarising lenses are parallel to each other, allowing 100% light transmission.) The test was repeated three times and the mean value of the polariser position determined. By means of the polariser calibration curve the ratio of light intensities transmitted to each eye was calculated as a percentage to give the brightness sense ratio. For example, if the better eye required only 60% of light transmitted for it to perceive equal brightness to the worse eye (which has 100% light transmission), then the brightness sense ratio is 60% – that is, the luminance perceived in the worse eye is only 60% of that in the better eye.

Spatial contrast sensitivity was determined by the Nicolet Optronics CS 2000 apparatus (Nicolet Biomedical Instruments). This system comprises a display monitor, a control console with keyboard, and an observer response box. It executes a standard von Bekesy tracking test of contrast sensitivity, whereby a number of electronically generated vertical sinusoidal grating patterns are displayed on a television screen. Each subject was seated at 3 metres giving a field size of 5°×4° for the television screen. The room luminance was comparable to the screen luminance. Each eye was tested in turn with the appropriate distance refractive correction when required. Pupil size was recorded but not altered. To minimise the ambiguity of this psychophysical test, the method of examination, the instructions given, and the patients' criteria of visible contrast were precisely standardised. In this study the machine was programmed to project sinusoidal gratings starting from low to high spatial frequencies. In anticipation of those test gratings the patients' contrast sensitivity may be higher than it would have been if the gratings were randomly displayed. However, since the same instructions and criteria of contrast perception were used, this would not affect the overall results and its interpretation. Six spatial frequencies were tested (0·5, 1, 3, 6, 11·4, and 22·8 cycles/degree), and the logarithm of contrast threshold for each frequency was computed. The modulation transfer function was determined in every case by plotting the logarithm of contrast threshold against spatial frequency.

## Results

Most of the control subjects had no significant ophthalmological history or findings except for two who had received antituberculosis therapy 20 years earlier and one who had had bilateral central serous retinopathy eight years before. Eight control subjects smoked more than 20 cigarettes a day. For none of these exceptions did the results obtained for the contrast sensitivity and brightness sense evaluation fall outside one standard deviation from the mean. One subject had unilateral cataract. The affected eye was not used in the study, which naturally precluded the use of this subject for interocular comparisons.

### VISUAL FIELDS

The possible score for visual field loss for each eye ranged from 0 to 114. No visual field loss was detected in any of the eyes of the control subjects. Among the patients with glaucoma a visual field score of more than 10 was found in 26 out of 28 patients (93%) (in 44 out of 52 glaucomatous eyes – 85%). The difference in the visual field scores between the two eyes was

TABLE I *Brightness sense score in normal subjects*

| *Age range (years)* | *Number of subjects* | *Brightness sense score (%)* | | | |
|---|---|---|---|---|---|
| | | *Mean* | *SD* | *95% Confidence limit** | *99% Confidence limit†* |
| 11–20 | 7 | 93·00 | 2·08 | 89·6 | 88·2 |
| 21–30 | 8 | 96·75 | 1·04 | 95·0 | 94·3 |
| 31–40 | 10 | 95·40 | 1·84 | 92·4 | 91·1 |
| 41–50 | 5 | 96·80 | 1·10 | 95·0 | 94·2 |
| 51–60 | 6 | 92·83 | 2·71 | 88·4 | 86·5 |
| 61–70 | 4 | 94·75 | 4·27 | 87·7 | 84·8 |
| All | 40 | 94·98 | 2·58 | 90·7 | 89·0 |

*95% Confidence limit given by mean − 1·65 SD.
†99% Confidence limit given by mean − 2·33 SD.

TABLE III *Abnormal contrast sensitivities in 52 eyes with chronic glaucoma. Results are classified abnormal if outside the 95% limit for the corresponding age group of control subjects*

| *Gratings (cycles/degree)* | *No abnormal* | *% Abnormal* |
|---|---|---|
| 0·5 | 8 | 15·4 |
| 1·0 | 7 | 13·5 |
| 3·0 | 8 | 15·4 |
| 6·0 | 11 | 21·2 |
| 11·4 | 9 | 17·3 |
| 22·8 | 1 | 1·9 |
| Sum of contrast sensitivities | 13 | 25·0 |

determined. Twenty-one of the 28 patients (75%) showed differences in visual field score greater than 5.

### BRIGHTNESS SENSE COMPARISON TEST

Table I details the brightness sense scores for the control subjects separated by age group. For all ages a brightness sense score of 89% corresponds to the 99 percentile limit. Analysis of variance confirmed that there were significant differences between age groups. Younger and older subjects gave lower brightness sense ratios corresponding to greater interocular differences, and the results of individuals in these age groups varied more widely. Subjects between 20 and 50 years of age provided higher scores with less variation.

Compared with the 99% confidence limit for age-matched controls, 24 of 28 glaucoma patients (86%) had abnormal ratios. In all these patients, the worse eye had a lower brightness perception. Two patients showed a 2 mm difference in pupil diameter at the time of examination, while the remainder had equal pupils. This may have affected their brightness sense to an indeterminate degree. However, if these two patients are removed from the group, the percentage of patients returning scores outside the 99% normal limit remains unchanged.

### CONTRAST SENSITIVITY

Table II illustrates the contrast sensitivity results for normal subjects. Where both eyes of patients were tested, the average of the sensitivities of the two eyes was taken for further analysis to deal with the possible correlation between values for pairs of eyes.[14]

TABLE II *Contrast threshold for normal subjects. For each spatial frequency the mean contrast threshold is given with the standard deviation below in brackets. The column headed 'sum' relates to the sum of thresholds for the 6 gratings*

| *Age range (years)* | *Number of subjects* | *Mean contrast threshold for various spatial frequencies** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | *0·5* | *1* | *3* | *6* | *11·4* | *22·8* | *Sum* |
| 10–19 | 6 | 1·16<br>(0·12) | 1·79<br>(0·06) | 2·18<br>(0·05) | 2·17<br>(0·18) | 1·91<br>(0·17) | 1·26<br>(0·40) | 10·5<br>(0·7) |
| 20–29 | 9 | 1·21<br>(0·12) | 1·97<br>(0·21) | 2·35<br>(0·19) | 2·27<br>(0·25) | 2·01<br>(0·28) | 1·63<br>(0·23) | 11·4<br>(0·9) |
| 30–39 | 10 | 1·26<br>(0·15) | 1·94<br>(0·20) | 2·34<br>(0·20) | 2·29<br>(0·17) | 1·99<br>(0·22) | 1·35<br>(0·29) | 11·2<br>(0·8) |
| 40–49 | 5 | 1·14<br>(0·16) | 1·87<br>(0·09) | 2·35<br>(0·26) | 2·24<br>(0·45) | 1·77<br>(0·57) | 1·43<br>(0·64) | 10·8<br>(2·0) |
| 50–59 | 6 | 1·14<br>(0·28) | 1·90<br>(0·25) | 2·18<br>(0·21) | 2·34<br>(0·19) | 1·94<br>(0·38) | 1·19<br>(0·63) | 10·7<br>(1·7) |
| 60+ | 5 | 1·23<br>(0·04) | 1·75<br>(0·15) | 1·94<br>(0·24) | 1·81<br>(0·24) | 1·40<br>(0·27) | 0·64<br>(0·54) | 8·8<br>(1·0) |
| All | 41 | 1·20<br>(0·16) | 1·89<br>(0·19) | 2·25<br>(0·23) | 2·22<br>(0·28) | 1·88<br>(0·35) | 1·30<br>(0·50) | 10·7<br>(1·4) |

*All contrast thresholds in this table are in logarithmic scales and are negative values. For simplicity the minus sign is not shown. Therefore the larger the value the greater is the contrast sensitivity.

Analysis of variance revealed that all groups of patients up to 60 years of age were closely similar but that there was a significant drop in contrast sensitivity for those over 60 years ($p<0{\cdot}001$). When the sensitivities for individual gratings were analysed, the over 60 years age group was found to have significantly poorer contrast sensitivity than younger subjects at spatial frequencies of 3 cycles/degree and higher ($p<0{\cdot}01$ for each grating). At the lower spatial frequencies employed, 0·5 and 1 cycle/degree, all age groups performed similarly.

The interocular ratios of sum contrast sensitivity were also calculated for normal controls. Expressing all values as a figure greater than 1 gave a mean of 1·09 and standard deviation of 0·06, with a 95 percentile limit of 1·19 (mean + 1·65 SD). Analysis of variance showed no significant differences of interocular ratio among the various age groups ($0{\cdot}05<p<0{\cdot}1$).

Table III shows the number of abnormal contrast sensitivities for the spatial frequencies tested and for sum contrast sensitivity for the 52 eyes with chronic glaucoma. The low and medium spatial frequencies were more commonly disturbed, while the higher frequencies were relatively spared. This would be expected, as high spatial frequencies correspond more closely to visual acuity. In total, 39% of glaucoma patients gave sum contrast sensitivity values below the normal limit (mean − 1·65 SD) for their age group. When the interocular ratios of the sum contrast thresholds are considered, 12 of the 28 patients (43%) had ratios outside the normal range.

### COMPARISONS OF DIFFERENT TESTS

An attempt was made to correlate brightness ratio with three other interocular measures – the visual acuity difference, the interocular ratio of sum contrast sensitivity, and the visual field score difference. For these comparisons Snellen acuities were transformed by the method of Westheimer, where the visual acuity was represented by the value of log (1/Snellen fraction).[15] Pearson correlation coefficients indicated no significant correlation between brightness ratio and either visual acuity difference or sum contrast sensitivity ratio ($p>0{\cdot}1$ in both cases), but there was a significant correlation with visual field difference ($0{\cdot}02<p<0{\cdot}05$) (Fig 2). Note that in all cases the direction of any observed difference was always that the poorer eye in the

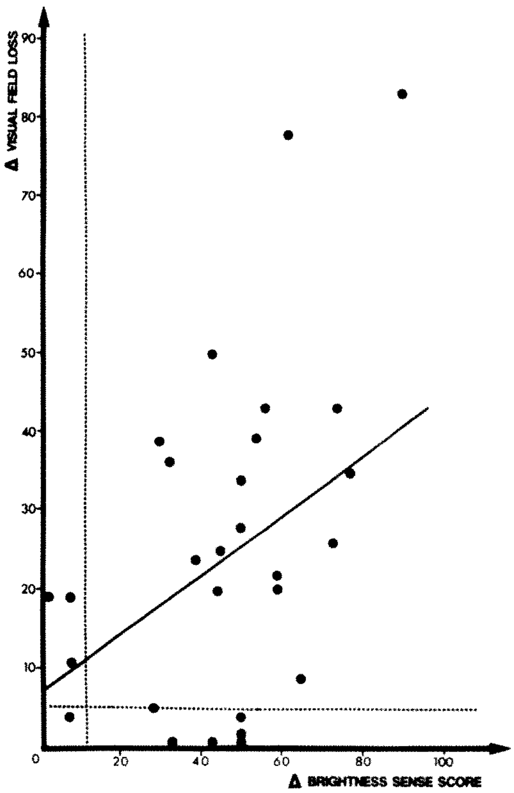

*Figure 2: Interocular difference in visual field loss versus interocular difference in brightness sense score for 28 glaucoma patients. The solid line was obtained by linear regression analysis. The dotted lines mark the normal limits (99%) of brightness score and interocular field difference.*

brightness discrimination test (that is, the one with 'dimmer' vision) was also poorer in terms of the other measures of visual function.

As can be seen in Fig 2, six patients outside the normal range of brightness ratio had no significant visual field score differences. Conversely, only three patients who had abnormal interocular visual field differences showed no abnormalities in significant brightness sense. However, as regards the presence of any glaucomatous field loss, three patients who had fairly similar field loss passed their brightness discrimination test. In contrast there were three other patients, with no significant field defects but with raised intraocular pressures and glaucomatous cupping, who gave abnormal brightness sense ratios.

## Discussion

The results of the present study indicate that, while 86% of glaucoma patients had abnormal brightness sense ratios, only 75% showed an interocular difference in visual field score. The sensitivity of the brightness sense comparison test comes very close to the presence of visual field loss in 93% of these patients. The high percentage of visual field loss was biased, as it was one of the criteria for patient selection and indeed for the diagnosis of glaucoma. The sum contrast sensitivity scores, however, were abnormal in only 39% of cases.

The brightness sense ratio test detects only a difference in the perception of brightness between the two eyes. Symmetrical impairment of optic nerve function in both eyes would not result in an abnormal brightness sense test. The results therefore reflect the asymmetric nature of optic nerve damage in glaucoma.

In a previous study of brightness sense in a variety of ophthalmic conditions,[10] 29 control subjects were assessed, but age variation was not examined. In the present study we have demonstrated significant variations of brightness ratio with age which is pertinent to future investigations. The control subjects aged between 20 and 50 years gave more reproducible responses than the older or younger subjects. Although brightness sense is severely impaired in optic nerve disease and is affected to a greater degree than visual acuity or other visual functions,[10] it is not specific to any particular optic nerve dysfunction.

A difference in pupillary size between eyes would be expected to produce a disparity in the perception of brightness due to differing degrees of retinal illumination. Ideally a correction factor for this should be calculated, but the large number of variables precludes the accurate estimation of such a factor.

There was a significant correlation between the interocular differences in brightness sense and the interocular differences in visual field loss within the central 30° of field. Clinical perimetry and the perception of brightness both depend on retinal sensitivity to light. This positive correlation indicates that the perception of brightness is probably an overall retinal function, with a greater influence being provided by the central 30° of retina.

A significant reduction in contrast sensitivity at medium to high spatial frequencies in elderly normal subjects was found. Similar findings have been reported previously.[5 16-18] This change in modulation transfer function is probably related to the loss of neuronal cells, either in the retina or along the visual pathway to the visual cortex. On the other hand the interocular ratio of sum contrast sensitivity did not show any marked variation with age, suggesting that loss of contrast discrimination tends to be symmetrical.

Only 39% of patients with glaucoma had abnormal contrast sensitivity, with a generalised depression at all spatial frequencies except the highest. This finding is in keeping with the presence of paracentral visual field loss and the late preservation of central visual acuity in glaucoma. In addition the present study indicates that 45% of glaucoma patients had abnormal interocular sum contrast sensitivity ratios. This ratio is therefore more sensitive as a means of detecting abnormality than the determination of sum contrast sensitivity for each eye, though still less sensitive than either brightness sense or visual field.

Most screening programmes for glaucoma involve measuring the intraocular pressure, recording the visual field, and assessing the optic disc.[1] Other screening tests which have been advocated include oculokinetic visual field assessment,[19] measurement of contrast sensitivity,[2 3] and nerve fibre bundle assessment with red-free filters.[4] However, the problems of high cost and complexity of multiple tests have militated against the development of screening programmes for glaucoma. As has been shown in this study, there were a few patients who were missed on the brightness discrimination test but had visual field defects and vice versa. It would appear that in the presence of a normal visual acuity (which would exclude most other causes of optic nerve dysfunction) an abnormal brightness sense test may prove to be a sensitive means of screening for glaucoma. The test is quick and easy to perform and does not require expensive equipment or technical skill. In addition the results are reproducible, as the patients give consistent results on repeated testing. Together with its sensitivity and low false positive rate it is potentially useful in mass glaucoma screening programmes, especially in the third world countries where trained personnel and financial assistance are limited. Compared to visual field screening, a sensitive and specific test in the diagnosis of glaucoma but which is time consuming and requires trained workers, this test may prove to be more practical.

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# Calculating the predictive power of the Henson field screener in a population at risk of glaucomatous field loss

Stephen A Vernon, Donald J Henry, Susan J Jones

**Abstract**

**Suprathreshold field screeners are in common use for the detection of glaucomatous field loss. The predictive power of a positive result (PP+) depends on the sensitivity and specificity of the screener in the population in which it is to be used. Using data from 755 normal individuals (1510 eyes), we calculated the PP+ of the Henson CFS2000 screening programme for a population aged 50 and over. 4·3% of normal eyes failed the screening programme. Ignoring one or two misses on the screening programme immediately adjacent to the disc reduced this figure to 1·3% and significantly improved the PP+ of the programme. Calculations of the PP+ at increasing glaucoma prevalence levels indicates this to be particularly relevant at low levels such as those encountered when screening middle aged and elderly populations. Optometrists should perform routine field analysis when screening for glaucoma provided they adhere to strict protocols.**

The 26-point Henson CFS2000 screening programme has been formulated to provide maximum sensitivity and specificity when screening for glaucomatous field loss. In a study on 94 suspect eyes the programme's sensitivity and specificity were calculated to be 90% and 88% respectively.[1] If an eye fails the screening programme, the operator is required to 'extend', testing a total of 66 or 132 points. This might appear to suggest that 12% of 'normal' eyes will require an extended field.

Sensitivity, a measure of the false negatives, and specificity, a measure of the false positives, are dependent on the certainty that a subject is positive or negative for the condition and on the prevalence of the disease in the population in which the test is to be used. Neither of these parameters of the efficiency of a test can be extrapolated from a small group of patients under suspicion to the general population at risk from glaucoma. Although the sensitivity of the test can be estimated when the prevalence of the disease is high in a sample, the specificity cannot.

In a recent study of the methods employed by optometrists when screening for glaucoma almost 80% used visual field analysis, though usually only when either the disc appeared abnormal or the intraocular pressure (IOP) was raised.[2]

In practice, when screening an individual for glaucomatous field loss, the optometrist needs to know the predictive power of a positive test (PP+). It is the chance that a positive result indicates a true positive identification of the disease process and is related to both sensitivity and specificity.

To calculate the predictive power of the screening programme on the Henson CFS2000 in a population, the following data are required from that population: (*a*) the incidence of screen failures in normal persons; (*b*) the prevalence of field defects from other causes; (*c*) the prevalence of glaucomatous field loss; (*d*) the false negative rate on screening eyes with field loss from glaucoma.

If (*c*) remains a variable, the PP+ for each value of (*c*) can be calculated only if (*a*), (*b*), and (*d*) are known. (*d*) has been determined to be 10% in a sample of eyes representative of those presenting to a hospital department with glaucomatous field loss.[1]

Therefore in order to estimate the predictive power of the Henson CFS2000 screening programme in the field we analysed the data on normal persons and patients with non-glaucomatous field defects identified on screening a general practice population aged 50 and over.

## Material and methods

The population of a general practice aged 50 and over were invited by letter to attend for glaucoma screening: 874 people (88·5% of those invited) attended. They were screened by the following tests: intraocular pressures with a non-contact tonometer, optic disc assessment by an experienced ophthalmologist, and visual field analysis. The only exclusions from screening were a history of dementia, glaucoma, or blind registration. Computer analysis of the practice records revealed no significant difference between those who did and did not attend when the following variables were examined: age, sex, family history of glaucoma, known hypertension, or known diabetes.

Intraocular pressures were measured with the Keeler Pulsair non-contact tonometer; the mean of four readings per eye was taken. Visual field analysis was then performed with the Henson CFS2000 as described below, followed by optic disc assessment. All eyes were examined by a single ophthalmologist (SAV) with a narrow beam direct ophthalmoscope through undilated pupils, discs being graded 'blind' as normal or suspicious. Any patient with an IOP >22 mmHg or having a suspicious optic disc was referred for a hospital assessment to determine the true status of the eye.

The visual fields were examined in the following manner with the screening programme of the Henson CFS2000:

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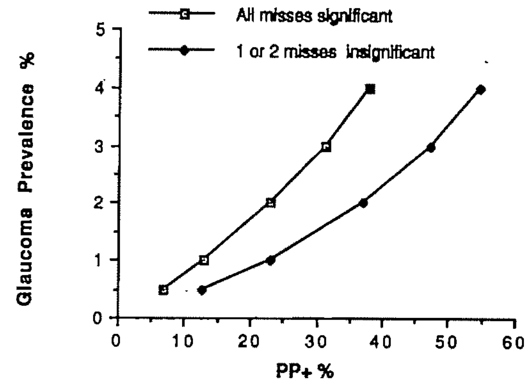
*Figure 1: Predictive power of a positive result on the Henson screening programme at different prevalence levels of glaucoma. Filled boxes determine the levels when one or two misses by the blind spot are considered insignificant.*



The test was performed either with single vision reading spectacles or unaided if these were not available. The right eye was always tested first. The minimum vision required to perform the test was defined as the ability to see the central target on the screen at 1/3 metre following the inbuilt ambient lighting check on the Henson apparatus. Central thresholds were then determined for each eye, threshold being taken as the lowest illumination required to detect 50% of the central targets in at least two of three presentations. The 26-point suprathreshold screening programme was then performed at 0·5 log unit above threshold. Three attempts were made at each setting before an eye was deemed to have missed a point. Any missed point on this test required the operator to extend to a 66-point test. Any eye which recorded a 'suspicious' or 'defective' field on the internal scale was classified as pathological.

Any eye that required an extended test was carefully examined to determine the presence of coexisting pathology that could have resulted in a screening failure.

Results are presented in terms of eyes rather than patients because Henson's data reflecting the false negative rate for the screening programme relate to eyes only. However, only patients in whom both eyes were normal on all accounts could contribute to the normal data.

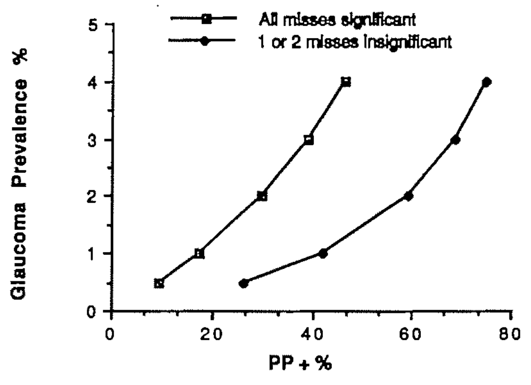
Calculations of predictive powers assume a 90% sensitivity for the screening programme.[1]

## Results

The number of eyes attempting the field test was 1748 (874 patients, mean age 65 years). Twenty-five failed to detect the central target due to poor central acuity; therefore 1723 eyes were tested.

One hundred and thirteen eyes (6·56%) from 98 patients (mean age 65·2 years) required an extended test. Seven were diagnosed as suffering from glaucoma at the hospital assessment and 106 (6·15%) were either normal or had other pathology. The 95% confidence limits (CL) on this percentage are 5·0 to 7·3%. A total of 52 eyes missed 1 or 2 points immediately by the blind spot, and 54 eyes (3·13%, 95% CL 2·3 to 4·0%) missed points elsewhere in the field.

*Figure 2: Predictive power of a positive result on the Henson screening programme at different prevalence levels of glaucoma when other ophthalmoscopically detectable causes of field loss are excluded. Filled boxes indicate the levels when one or two misses by the blind spot are considered insignificant.*



Forty-two eyes from 33 patients (mean age 70·8 years) required an extended field as a result of non-glaucomatous disease, 31 eyes falling into the pathological category as defined above. In only three of the others was the defect limited to 1 or 2 points immediately adjacent to the blind spot.

Eyes classified as normal on all three screening parameters numbered 1510 (755 patients). The mean time taken to perform the screening programme on both eyes of these patients was 2 minutes 30 seconds. Sixty-four eyes (4·3%, 95% CL 3·3 to 5·3%) from 56 patients (mean age 61·4 years) failed the field screening programme, eight patients failing in both eyes. Of the remaining 54 eyes, 16 were right eyes and 38 were left ($0{\cdot}05>p>0{\cdot}01$ by $\chi^2$ analysis). Forty-five eyes missed only 1 or 2 points immediately adjacent to the blind spot and none of these missed other points on the 66-point extended field ($p<0{\cdot}0001$).

An eye failing the screening programme where the defect is limited to one or two misses immediately adjacent to the blind spot is therefore 11·5 times more likely to be normal than to have any demonstrable pathology. None of the eyes later confirmed as suffering from glaucoma missed spots immediately adjacent to the blind spot as the sole reason for failing the screening test.

The PP+ of the Henson screening programme used in isolation in a population with a 1% ocular prevalence of glaucomatous field loss comprising 10 000 eyes from persons aged 50 and over can be estimated as follows:

0·9% of 10 000 will fail the screen because they do have glaucoma=90. However, 6·15% of the 9900 non-glaucomatous eyes will also fail the screen=609.

$$PP+=\frac{1}{\frac{609}{90}+1}\times 100=12{\cdot}9\%.$$

This figure assumes any point missed at 0·5 log unit over threshold to be significant. The 95% CL are 11·1 to 15·4%.

If one or two misses immediately adjacent to the blind spot are considered insignificant, the PP+ at 1% glaucoma prevalence rises to 23·1% (95% CL 18·5 to 28·3%).

Figure 1 shows the manner in which the PP+ of the Henson screening programme would be expected to change in populations with increasing prevalence of glaucomatous field loss. Calculations assume no change in the prevalence of other conditions causing field loss.

Figure 2 indicates the change in PP+ when other ophthalmoscopically recognisable conditions causing field loss are excluded.

## Discussion

This study aimed to calculate the predictive power of a positive field screen on the Henson CFS2000 in a population of middle aged and elderly persons. The study design attempted to reduce false negatives to a minimum.

The results would appear to confirm that it is reasonable to ignore misses on the screening programme immediately adjacent to the blind spot. This would reduce the number of normal eyes in a population failing the Henson screening test from between 3·3 and 5·3% to between 0·7 and 1·8% (applying 95% confidence limits). An isolated apparent enlargement of the blind spot on bowl perimetry was originally taken to be a sign of an early functional defect,[3] but this has since been abandoned.[4]

It is interesting that the left eyes of normal persons were statistically more likely than right eyes to fail the screening test employed in our study. However, when misses immediately adjacent to the blind spot are removed from the analysis, the asymmetry loses its significance. This indicates that we may be observing a fatigue effect, as the left eye was always the second to be tested, small changes in fixation producing an apparent enlargement of the blind spot. Fatigue effects are common in longer psychophysical tests but would not be expected in tests of such short duration as three or four minutes.[5] Moreover, fatigue would be expected to occur earlier, as age and the time taken to complete the test increase.[6] However, the mean age of normal persons who failed the field screen was not greater than those who passed.

Accurate refraction of all subjects was not considered feasible in a study such as ours. We therefore performed field analysis with either single vision reading spectacles or unaided, preferring to eradicate possible false positives from the edge of bifocal segments. The question of the effect of uncorrected refractive errors therefore remains.

In static perimetry, peripheral threshold sensitivity decreases linearly with increasing eccentricity, the slope of the decline being approximately parallel when increasing optical errors are simulated.[7] The Henson test, in effect, compares peripheral sensitivity with predetermined paracentral thresholds, and therefore an increased paracentral threshold from uncorrected optical errors would not be expected to produce false positive or negative results in the Bjerrum areas.

Some of the screening programme failures, with points missed around the disc, may be due to uncorrected optical errors producing artificial enlargement of the blind spot. The excess of left eyes in this group indicates that, unless left eyes in our unaided subjects had significantly greater optical errors, this effect is minimal. Other factors such as the method of padding the left eye during testing of the right eye may explain this phenomenon, but these cannot be determined from the results of this study.

Our study population is known to be representative of the population of Nottingham. Despite this, care should still be taken when interpreting the results. Alterations in any of the variables may have a profound effect on the PP+. In particular it is very dependent on a strict screening protocol being observed.

The prevalence of glaucomatous field loss is known to increase with age[8] and in certain racial groups.[9] Although the PP+ will always increase with a higher population prevalence of the disease, it will not do so in a linear manner. For example other conditions producing field loss may also be more prevalent. However, an experienced, confident ophthalmoscopist will be able to increase the PP+ of the screening programme by recognising these 'false positives.' For example, in a similar population with a glaucoma prevalence of 2%, the PP+ would rise from 23%, if any miss was considered significant, to 59% if other causes of field loss are identified and misses by the blind spot are ignored (see Figs 1 and 2).

As recently as the early 1980s 33% of glaucoma sufferers presented with advanced field loss in at least one eye.[10] In a recent study of optometrists who screened for glaucoma only 8% routinely used visual field analysis.[2] It has been estimated that 50% of patients with glaucomatous eyes present with an IOP within the accepted normal range.[8] Moreover, the optic disc in early glaucoma is known to be notoriously difficult to assess.[11] Consequently it is perhaps not surprising that patients continue to present with advanced disease. Indeed, it is not uncommon for such patients to report that they have been passed as normal by an optometrist within a few months of presenting to the hospital eye service.

Although field analysis is likely to detect only those eyes that have lost more than 50% of their nerve fibres,[12] it is these eyes which require urgent attention if vision is to be preserved.[13] Our study lends weight to the argument that routine central field analysis should be performed by optometrists during their glaucoma screening protocol on their middle aged and elderly clients. We have shown it can be completed quickly with acceptable predictive power levels, provided a strict protocol is observed.

The authors have no financial interest in the Henson CFS2000 field screener. This work was supported in part by grants from the International Glaucoma Association and MSD Ltd. The screening equipment used in this study was kindly loaned by Keeler Ltd.

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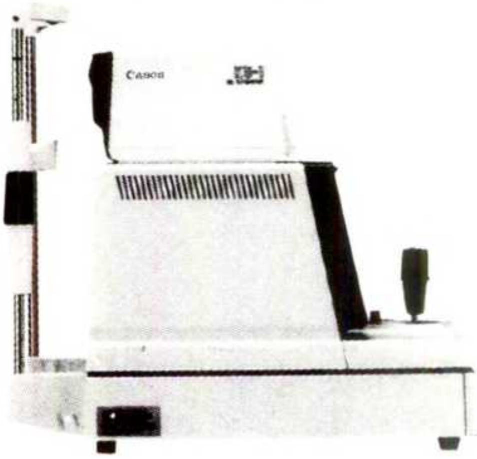

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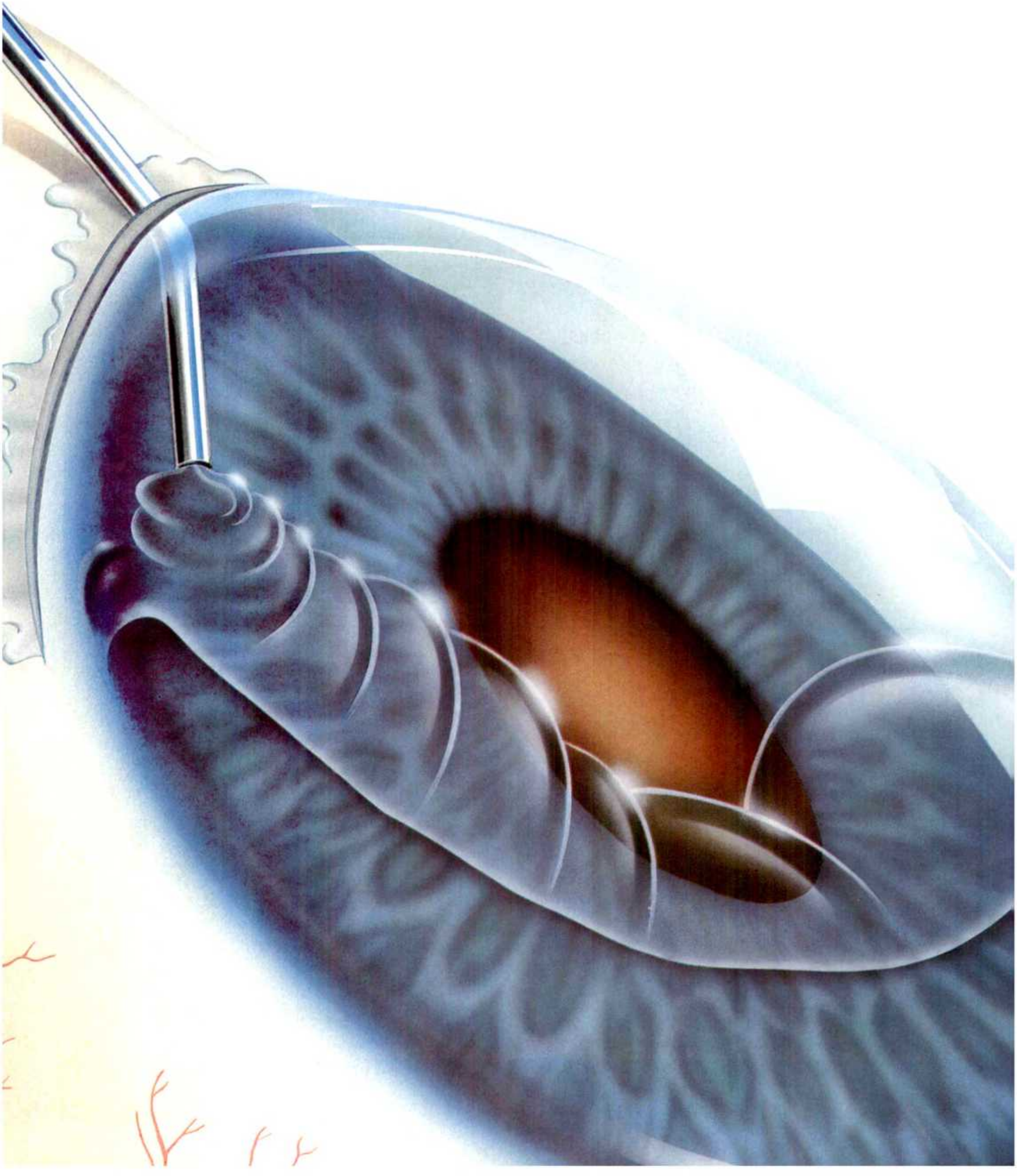

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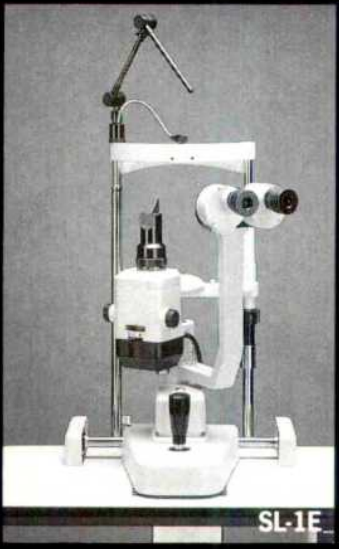

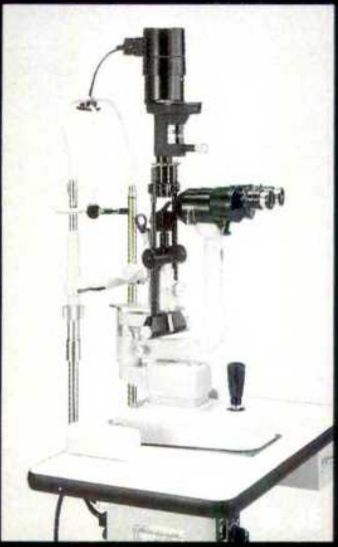

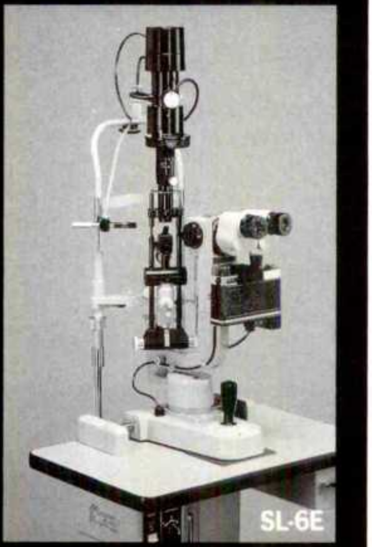

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*British Journal of Ophthalmology*, 1990, 74, 223–227

# Glaucoma in patients with uveitis

William C Panek, Gary N Holland, David A Lee, Robert E Christensen

**Abstract**

**The records of 100 patients (161 eyes) with uveitis were reviewed retrospectively to determine the prevalence of increased intraocular pressure, the forms of uveitis most commonly associated with glaucoma, and the forms that require specific glaucoma therapy. Secondary glaucoma was present in 23 patients (31 eyes): three of 24 patients with acute uveitis (three eyes, 12% of acute uveitis patients) and 20 of 76 patients with chronic uveitis (28 eyes, 26% of chronic uveitis patients). Eighteen patients (26 eyes, 78% of glaucoma patients) with chronic uveitis required long-term medical therapy to control intraocular pressure. Three patients (three eyes, 12% of glaucoma patients) with acute uveitis required short-term therapy to control intraocular pressure. The remaining two patients had transient increases in intraocular pressure that did not require treatment or that responded to treatment of intraocular inflammation alone. One patient with chronic uveitis (two eyes, 4% of glaucoma patients) required filtering surgery. At least five patients (eight eyes, 22% of glaucoma patients) had glaucomatous visual field defects. The results of this survey are consistent with the concept that secondary glaucoma is a management problem in patients with anterior segment inflammation and chronic rather than acute uveitis. An algorithm for the management of increased intraocular pressure in patients with uveitis is proposed.**

Particularly complex management decisions arise when intraocular inflammation is coupled with increased intraocular pressure. The delicate tissues of the anterior segment may become swollen, scarred, and distorted, or rendered malfunctional by the inflammatory response,[1] leading to increase of intraocular pressure, glaucomatous damage to the optic nerve, and subsequent loss of visual field. Steroids, the mainstay of treatment for uveitis, may also cause increased intraocular pressure.[2] The physician must evaluate carefully the effects of both disease and therapy in order to provide proper management for patients with uveitis and glaucoma.

This study was undertaken to obtain data on the prevalence of increased intraocular pressure in patients with uveitis and to identify the forms of uveitis most commonly associated with glaucoma and that require specific glaucoma therapy. With such information rational approaches to the management of uveitis-related glaucoma can be planned.

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## Subjects and methods

The records of 100 consecutive patients with uveitis referred to and examined by one author (GNH) at the Jules Stein Eye Institute, UCLA School of Medicine, were reveiwed retrospectively. Uveitis was identified by the presence of inflammation involving any intraocular structure at the time of examination or by a well documented history of intraocular inflammation. Excluded were patients with self-limited anterior chamber inflammatory reactions during a one-month period following intraocular surgery, patients with neoplastic disease mimicking uveitis ('masquerade syndromes'), and patients with cytomegalovirus (CMV) retinopathy.*

Each case was examined for location of inflammation, disease chronicity, and the presence or history of increased intraocular pressure. For the purpose of this study, the patients were considered to be glaucoma suspects or to have uveitic glaucoma if intraocular pressure was above 21 mm Hg on more than one examination at UCLA, or if the patient was receiving antiglaucoma therapy at the time of initial examination at UCLA and previously had a well documented increase in intraocular pressure concurrent with intraocular inflammation. No patients had a history of pre-existing primary open angle glaucoma.

The cases were divided into acute and chronic uveitis as defined by the International Uveitis Study Group.[3] Cases of acute uveitis were less than three months in duration and cases of chronic uveitis were of three months or more.

## Results

There were 161 eyes with uveitis among the 100 patients investigated in this study (Table 1). Twenty-four patients (34 eyes) had acute uveitis and 76 (127 eyes) had chronic uveitis. All the patients had cells and flare in the anterior chamber, indicating anterior segment inflammation, regardless of the primary site of disease. Of the patients with acute uveitis all had primary inflammation of the anterior segment except three, who had toxoplasmic retinochoroiditis with secondary iridocyclitis. Eleven patients with chronic uveitis had intermediate uveitis (pars planitis). Of the remaining 65 patients with chronic uveitis, one with Vogt-Koyanagi-Harada syndrome, one of three with sarcoidosis, and one of 33 with uveitis of unknown cause had inflammation of the posterior segment; all others had inflammation of the anterior segment alone.

Twenty-three patients (31 eyes) had secondary uveitic glaucoma by our criteria. Three patients (three eyes) had acute uveitis and 20 patients (28 eyes) had chronic uveitis. Glaucoma occurred in

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*The author examines a large number of patients with CMV retinopathy enrolled in clinical research protocols. They would have made up a disproportionately large percentage of the consecutive uveitis cases had they been included. No patient with CMV retinopathy had an increased intraocular pressure.

TABLE I *Patients with uveitis and increased intraocular pressure (IOP)*

| *Diagnosis* | *Number of patients* | *Total eyes with inflammation* | *Patients with increased IOP* | *Total eyes with increased IOP* |
|---|---|---|---|---|
| *Acute uveitis* | | | | |
| HLA B27+ | 11 | 15 | 0 | 0 |
| HLA B27− | 9 | 13 | 0 | 0 |
| Toxoplasmosis | 3 | 5 | 2 | 2 |
| Posner-Schlossman syndrome | 1 | 1 | 1 | 1 |
| Total | 24 | 34 | 3 | 3 |
| *Chronic uveitis* | | | | |
| Unknown cause | 33 | 61 | 8 | 13 |
| Intermediate (pars planitis) | 11 | 20 | 1 | 1 |
| Juvenile rheumatoid arthritis | 7 | 14 | 3 | 5 |
| Intraocular lens-associated | 6 | 6 | 2 | 2 |
| Fuchs' heterochromic iridocyclitis | 5 | 6 | 2 | 2 |
| Herpes simplex virus associated | 5 | 5 | 2 | 2 |
| Sarcoidosis | 3 | 6 | 1 | 2 |
| Syphilis | 3 | 5 | 0 | 0 |
| Herpes zoster virus associated | 2 | 2 | 1 | 1 |
| Vogt-Koyanagi-Harada syndrome | 1 | 2 | 0 | 0 |
| Total | 76 | 127 | 20 | 28 |

12% of patients with acute uveitis and in 26% of patients with chronic uveitis. There was no statistically significant difference in the incidence of glaucoma between these two groups. All 23 glaucoma patients had at some time undergone steroid therapy – oral, topical, or periocular. Treatment regimens at the time of this review varied from prednisone 60 mg orally every day combined with prednisolone acetate 1% solution every hour to fluorometholone 1% solution every other day. Only one patient with glaucoma was off steroid therapy. No cases of glaucoma were shown to be secondary to steroid response.

Toxoplasmic retinochoroiditis was the only form of posterior uveitis in which secondary anterior segment inflammation resulted in increased intraocular pressure. Posner-Schlossman syndrome was the only acute primary anterior segment disorder that was found to be associated with increased intraocular pressure. All the other patients had chronic uveitis, either primary anterior segment inflammation alone or panuveitis. All the patients with bilateral uveitis who developed glaucoma did so in both inflamed eyes. At least five patients (eight eyes, 22% of glaucoma patients) had glaucomatous visual field defects.

Twenty-one patients (29 eyes, 91% of glaucoma patients) received antiglaucoma medications for control of intraocular pressure. Eighteen patients (26 eyes, 78% of glaucoma patients) required continuous, ongoing therapy; all had chronic uveitis. The other three patients (three eyes, 13% of glaucoma patients), all of whom had acute uveitis, required brief medical therapy only during the initial period of inflammation. The remaining two patients with glaucoma (two eyes, 9% of glaucoma patients), both of whom had chronic anterior uveitis, did not require medical therapy; they had histories of transient, self-limited increases in intraocular pressure that responded to treatment of inflammation alone. One patient (two eyes, 4% of glaucoma patients) with chronic uveitis required filtering surgery to lower the intraocular pressure.

## Discussion

The spectrum of uveitic disorders in this series is consistent with that seen in other referral practices.[4] Uveitis may be complicated by a variety of secondary problems including cataract formation, synechiae, macular oedema, and glaucoma. In the present series glaucoma was one of the most common complications that required therapeutic intervention.

The factors most commonly associated with problems in the management of glaucoma were disease chronicity and primary anterior segment inflammation. Toxoplasmic retinochoroiditis was the only disorder in which secondary anterior segment inflammation resulted in rises of intraocular pressure requiring medical therapy. Increased intraocular pressure associated with acute uveitis was not a significant management problem, generally responding well to brief periods of medical therapy. Glaucoma associated with chronic uveitis usually required prolonged medical therapy for control of pressure. Even with chronic uveitis, however, treatment of inflammation alone brought intraocular pressure under control in some cases. Visual field loss was a problem only in patients with chronic uveitis.

In this group of referral patients it is possible that the incidence of raised intraocular pressure among patients with acute uveitis was underestimated. A transient rise in pressure associated with the onset of intense inflammation that resolved with the initiation of anti-inflammatory therapy by referring physicians may have been missed. It is unlikely, however, that such transient increases in pressure pose a serious problem to the eye.

### PATHOPHYSIOLOGY OF UVEITIC GLAUCOMA

The status of the anterior chamber angle gives an important anatomical division into either closed or open angle types of glaucoma, and has important therapeutic and prognostic implications. In patients with uveitis the angle can be closed as a result of posterior synechiae producing pupillary seclusion and iris bombé.[5] Angle closure also can occur without pupillary block. It can result from peripheral anterior synechiae (an iridotrabecular adherence-associated inflammation of iris and angle structures) and sometimes inflammatory nodules in the angle.[1,6] In addition rubeosis iridis leading to fibrovascular scarring and closure of the angle can occur in patients with uveitis.[7] In this series no cases of angle closure were seen, indicating that this mechanism may occur infrequently in patients receiving anti-inflammatory therapy.

Increased intraocular pressure associated with a clinically open angle involves microscopical changes with the trabecular meshwork. Postulated mechanisms include (1) mechanical blockage of the trabeculum by serum components that are liberated because of vascular incompetence;[8] (2) hypersecretion associated with prostaglandin mediated vascular hyperpermeability;[9,10] (3) overtaxing of outflow mechanisms by protein that interferes with active transport;[11] (4) inflammation of the trabeculum itself with swelling that causes impaired outflow;[6] (5) damage to trabecular endothelial cells by the inflammatory process;[12] (6) mechanical obstruction of outflow by precipitates on the meshwork;[13] (7) sclerosis of trabecular meshwork as a result of chronic inflammation;[5] or (8) obstruction of the trabeculum by a hyaline membrane.[5]

Steroid therapy is also a potential cause of raised pressure,[2,14,15] though in the present series no cases of steroid induced glaucoma were recorded. Steroid induced glaucoma is very similar to primary open angle glaucoma,[16] occurring slowly over weeks to months. Occasionally, however, an acute increase in pressure is noted. In all cases the trabeculum is clinically normal in appearance. Cessation of steroids usually leads to a return to normal of the pressure.[16]

In many patients with anterior segment inflammation who are receiving chronic steroid therapy it is not clear whether increased intraocular pressure is due to the effect of the inflammation or steroids. There is not always a relationship between the amount of inflammation, as measured by cells and flare, and inflammation induced rise of intraocular pressure. One therefore cannot predict in which patients intraocular pressure will drop when steroid therapy is increased. The authors have seen patients with only 1+ cells in the anterior chamber who had a dramatic drop in pressure with an increased dosage of steroids.

## GLAUCOMA ASSOCIATED WITH SPECIFIC UVEITIC DISORDERS

Many different types of uveitis have been associated with glaucoma, but certain disorders may have a relatively higher risk. For example, glaucoma is believed to be the major long term threat to vision in patients with Fuchs' heterochromic iridocyclitis.[17-19] Though frequently intermittent and well controlled initially, glaucoma may become chronic and difficult to treat.

Glaucoma is also a major component of the Posner-Schlossman syndrome (glaucomatocyclitic crisis).[20] Though inflammatory signs may be minimal, rises in intraocular pressure may be severe, leading to blurred vision, haloes, and ocular discomfort. Pressures of 40–50 mmHg are not uncommon. Raitta and Vannas believe that there may be a relationship between this syndrome and the eventual development of primary open angle glaucoma.[21]

Segmental iris ischaemia, demonstrated on

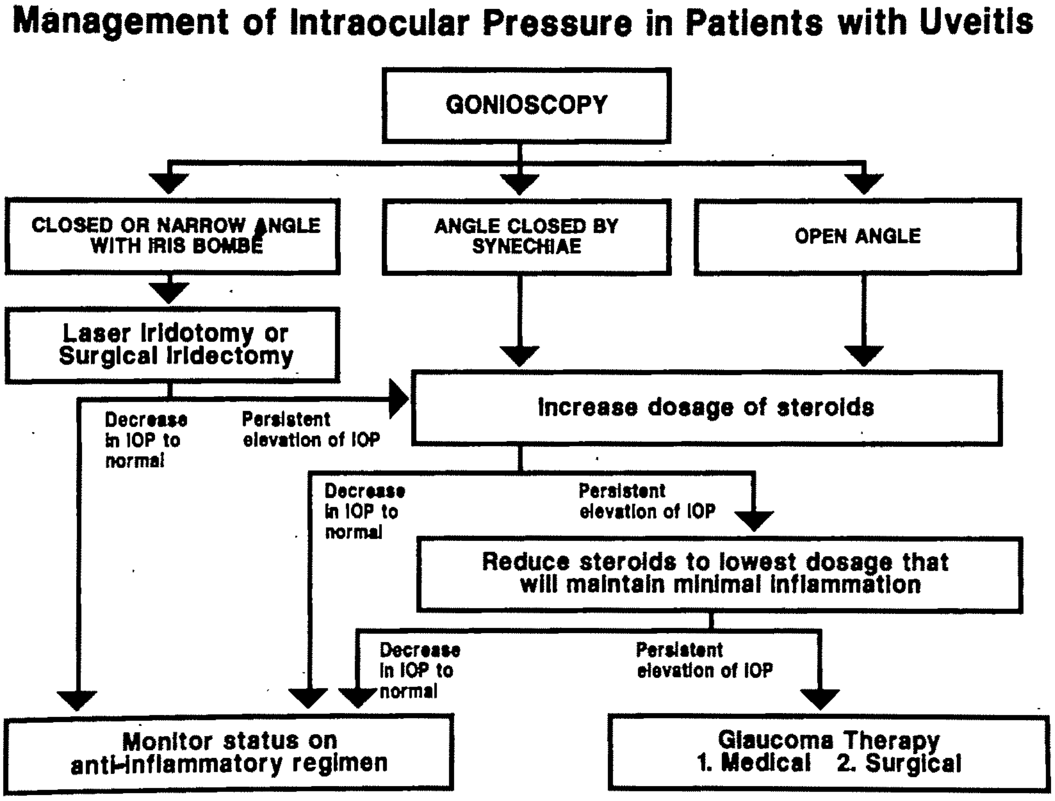
Management of Intraocular Pressure in Patients with Uveitis
GONIOSCOPY
CLOSED OR NARROW ANGLE WITH IRIS BOMBE
ANGLE CLOSED BY SYNECHIAE
OPEN ANGLE
Laser Iridotomy or Surgical Iridectomy
Decrease in IOP to normal
Persistent elevation of IOP
Increase dosage of steroids
Decrease in IOP to normal
Persistent elevation of IOP
Reduce steroids to lowest dosage that will maintain minimal inflammation
Decrease in IOP to normal
Persistent elevation of IOP
Monitor status on anti-inflammatory regimen
Glaucoma Therapy
1. Medical 2. Surgical

Figure 1: Algorithm for the management of raised intraocular pressure in patients with uveitis.
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fluorescein angiography, implies a vascular cause or the Posner-Schlossman syndrome.[21] Vasculature incompetence could be associated with a release of prostaglandins, inflammation and a subsequent rise in intraocular pressure.[22] Oral indomethacin and subconjunctival polyphloretin, both prostaglandin inhibitors, have been shown to lower intraocular pressures during attacks.[22]

The prognosis for control of intraocular pressure in patients with glaucomatocyclitic crisis is good.[23] Current treatment recommendations include both topical steroid therapy to reduce inflammation and antiglaucoma medications to control pressure during acute attacks. Future modes may include antiprostaglandin therapy as well as treatment to modify vascular instability.[21]

The chronic uveitis associated with systemic disease is frequently complicated by severe glaucoma.[24] The glaucoma associated with juvenile rheumatoid arthritis commonly occurs with open angles but may be of the pupillary block, secondary angle closure type, as a result of the formation of posterior synechiae.[25 26] When glaucoma occurs in patients with sarcoid uveitis, medical and surgical therapy may have only limited success.[27 28]

Glaucoma may be a prominent feature of the uveitis that results from ocular infections. The prevalence of secondary glaucoma associated with toxoplasmic retinochoroiditis was reported to be 12% in one series.[29] Although the glaucoma in that group was described as transient, a more recalcitrant form may occur with severe infections.

Herpetic uveitis may be particularly prone to the development of glaucoma.[30] In severe cases long term antiglaucoma therapy may be indicated even after active inflammation has subsided.[30] Herpes simplex virus keratouveitis is often associated with a raised intraocular pressure; Falcon and Williams reported glaucoma in 28% of 183 patients.[30] Postulated mechanisms include both blockage of the trabeculum with inflammatory debris and inflammation of the trabeculum.[31] Townsend and Kaufman found that glaucoma was also a problem in experimental herpes simplex virus keratouveitis in the rabbit.[32] Secondary glaucoma was attributed to a mononuclear cellular infiltrate in the angle; in addition occasional peripheral anterior synechiae were seen in severe cases.

Secondary glaucoma also can be a serious problem in patients with herpes zoster virus keratouveitis; Womack and Liesegang reported uveitic glaucoma in 10 of 37 patients.[33] The pathophysiology is probably similar to that associated with herpes simplex virus keratouveitis.[30]

Uveitis may complicate the use of iris supported or anterior chamber intraocular lenses,[34] more likely as a result of mechanical factors such as chafing of the lens against ocular tissues. The smouldering low-grade uveitis may lead to secondary glaucoma; Ellingson described a distinct syndrome of uveitis, glaucoma, and hyphaema in such patients.[35] The prognosis for the control of pressure is good if inflammation can be controlled.

## EVALUATION AND TREATMENT OF UVEITIC GLAUCOMA

The treatment of intraocular inflammation itself is an important component of glaucoma management, because it prevents damage to angle structures and blockage of outflow channels by inflammatory material and thereby maintains normal aqueous outflow.[36] In one case of the present series the control of inflammation by chlorambucil in a patient having a 20-year history of uveitis associated with juvenile rheumatoid arthritis also resulted in lowering of intraocular pressure that could not be controlled by antiglaucoma medications alone.

There may be special considerations in the medical management of glaucoma in patients with uveitis. Miotics such as pilocarpine should be used with caution in inflamed eyes, because they may exacerbate the underlying inflammatory process.[36] The ocular hypotensive effect of epinephrine is inhibited by cyclo-oxygenase inhibitors such as indomethacin. Patients using epinephrine should be monitored for this pressure-raising effect in those rare cases in which non-steroidal anti-inflammatory agents are used in the management of uveitis.[37]

The laser and surgical treatment of glaucoma in patients with uveitis also involves special considerations. Laser iridotomy may be difficult to perform in inflamed eyes[36] and may cause scarring. Should surgical peripheral iridectomy be required in cases of uveitis for the treatment of pupillary block glaucoma, surgical section or large peripheral iridectomies should be considered.[36] The efficacy of laser trabeculoplasty varies in these patients[38] and may lead to a worsening of both inflammation and glaucoma.

For patients with chronic inflammatory glaucoma some authors[36 39] recommend trabeculodialysis as the procedure of choice. Success rates as high as 63% with this technique have been reported, in contrast to rates of 18% with standard filtration surgery.[39]

Adjunctive methods of treatment are under investigation to decrease postoperative inflammation and fibrosis after glaucoma filtering surgery. They include the use of locally administered agents such as 5-fluorouracil[40] and triamcinolone[41] in the preoperative and postoperative periods. In future these regimens may be shown to improve filter survival in patients with uveitic glaucoma.

On the basis of these concepts the authors propose a stepwise approach to the evaluation and treatment of increased intraocular pressure in patients with uveitis (Fig 1). Because steroid associated glaucoma is apparently uncommon, and because the effect of prolonged or increased inflammation is potentially worse than a transient steroid induced rise in intraocular pressure, one should first increase steroid dosage and observe both intraocular pressure and inflammation. In cases where severe glaucomatous nerve damage previously exists, antiglaucoma therapy may be included while steroids are increased and then withdrawn if pressure decreases.

If intraocular pressure remains unchanged or rises with increased steroids, and inflammation is stable or improved, steroid therapy should be reduced to the least amount that will maintain the lowest achievable level of inflammation. If intraocular pressure remains raised as steroid therapy is reduced, glaucoma therapy is initiated. While the modes of therapy may be dictated by the presence of inflammation, the intensity of treatment – as with all forms of glaucoma – is based on the level of intraocular pressure, visual field changes, and status of the optic nerve.

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# Ultrastructural distribution of collagen types I–VI in aging human retinal vessels

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## Abstract

**Retinal vessels from freshly enucleated human eyes were classified into three stages of the hyalinisation process. The distribution of collagen types I–VI within the vessel walls was studied ultrastructurally by immunogold labelling combined with the tissue preparation techniques of cryoultramicrotomy and London resin white embedding. Collagen types I, III, IV, V, and VI were found in large vessels, types I, IV, and V plus small amounts of III and VI in small vessels, and types I, IV, and V in capillaries. Hyalinised vessel walls consisted mainly of types I, IV, and VI collagen.**

The changes which occur as part of normal aging have been documented at the level of light microscopy[1] and essentially consist of progressive replacement of myocytes by collagenous tissue. This process of hyalinisation was explored at the level of electron microscopy, and this revealed obvious reduplication of the basement membrane-like material and deposition of 65 nm banded collagen.[2] The significance of hyalinisation in blood vessels has been explored in terms of neovascularisation.[3-5] It is a reasonable hypothesis that a change in the ground substance may modify endothelial cell proliferation in the presence of retinal ischaemia and the subsequent release of vasoformative factors.[2-5] It is therefore important that the new technology of immunogold labelling be applied to the study of collagen types which are present in aging blood vessels, and in this presentation a preliminary outline of the distribution of collagens I, III, IV, V, and VI will be described.

## Materials and methods

Human retinal tissue was obtained from freshly enucleated eyes of eight patients with choroidal melanoma and four freshly enucleated eyes from patients with other disorders (for details see Table I).

TABLE I *Clinical details. Indications for enucleation and classification of retinal vascular disease*

| *Age* | *Sex* | *Indication for enucleation* | *Classification of retinal vessels* |
|---|---|---|---|
| 81 | F | Secondary glaucoma | A |
| 64 | F | CM | C |
| 36 | M | CM | A |
| 28 | M | CM | A |
| 68 | M | CM | A |
| 52 | M | CM | B |
| 63 | F | CM | B |
| 64 | M | CM | A |
| 68 | M | Corneal injury | C |
| 64 | F | Metastatic carcinoma | B |
| 63 | M | CBM | B |
| 76 | M | CM | C |

CM=choroidal melanoma. CMB=ciliary body melanoma.

The eyes were immersed immediately after enucleation in a freshly prepared fixative solution of 4% paraformaldehyde plus 0·2–1·0% glutaraldehyde in 0·1 M Sorensen's phosphate buffer or cacodylate buffer pH 7·2. After 10 minutes the eyes were opened to allow for rapid penetration of the fixative into the eye. A minimum of 10 blocks were dissected out from every level (primary, secondary, and tertiary) of the vascular tree with regions of arteriole-venule crossover points being preferred. Control tissue was taken from the cornea and sclera. The blocks were washed three times in buffer (5 min) and allocated for cryoultramicrotomy, London resin (LR) white embedding, and processing in Araldite for conventional electron microscopy. LR white is a hydrophilic resin that can be used for immunocytochemical studies owing to its property of preserving tissue antigenicity.

### CRYOULTRAMICROTOMY

The blocks were infused in 2·3 M sucrose for at least two hours at 4°C, mounted on cryo pins and snap frozen in liquid nitrogen. Ultrathin frozen sections were cut at −85°C on a Reichert Jung FC4D cryoultramicrotome (Cambridge Instruments) and transferred to 200 mesh carbon Formvar composite nickel grids by means of a 2·3 M sucrose drop and stored on Sorensen's buffer at 4°C until commencement of the immunolabelling procedure.

### PLASTIC EMBEDDING

The blocks allocated for LR white embedding were prepared by the following steps, all at 4°C: quenching in 0·5 M $NH_4Cl$ in Sorensen's buffer for at least two hours, washed twice in buffer, dehydrated in two one-hour changes of 70% alcohol and infiltrated with two one-hour changes of LR white hard grade resin, and polymerised at 50°C for 24 hours in size sealed gelatin capsules. Gold coloured ultrathin sections were cut on an LKB Ultrotome Nova (Cambridge Instruments), mounted on 200 mesh nickel grids, and left to dry for 10 min before storing on 50 mM Tris buffer pH 7·2 at 4°C.

### IMMUNOCYTOCHEMISTRY

The antibody dilutions in Tris buffer plus 1% bovine serum albumin (BSA) determined by previous experimental work, were 1:40–1:150 for types I, II, III, and V and 1:120 for type IV. The antibodies used against these collagens were raised in goats against both human and bovine collagen and were supplied by Southern Biotechnologies Inc. (UK distributors: Bionuclear

Services Ltd). Rabbit antibodies against type VI collagen were supplied by Heyl, West Germany, and were used at concentrations between 1:25 and 1:600.

The precise immunocytochemical procedure has been described by Konstas *et al.*[6]

### CONTROLS

Normal goat serum negative controls for collagens I–V and normal rabbit serum negative controls for type VI collagen (both from Sigma) were concurrently conducted at the same dilutions. Human cornea was used as a positive control for collagen types I, IV, and V, and sclera provided a positive control for collagen types I and III.

## Results

An arbitrary classification was used to distinguish the degree of hyalinisation in venules and arterioles. Owing to considerable variation within an individual eye, retinal vessels were placed into one of three grades of the hyalinisation process by an arbitrary classification by light microscopic examination of toluidine blue stained semithin plastic sections. Category A (Fig 1a) consisted of what was thought to be ostensibly normal vessels in which normal myocytes were identified. In Category B (Fig 1b) the walls were significantly thickened but still possessed several layers of myocytes, whereas category C (Fig 1c) consisted of grossly thickened walls with very few myocytes. Five of the cases studied were placed into category A, four into category B, and three into category C.

In all three categories into which the vessel wall was categorised major vessels were found to contain collagen types I, III, IV, V, and VI. Smaller branch vessels contained types I, IV, and V collagen, with diminished amounts of types III and VI. The connective tissue round capillaries contained types I, IV, and V only. Types III and V collagen were found in normal and hyalinised vessels. However, the thickening of hyalinised vessel walls was found to be due to excessive amounts of type I, IV and VI. Type II collagen was consistently absent at all levels of the retinal vasculature.

Type IV labelling was restricted to basement membranes round myocytes and lining the basal aspect of endothelial cells in larger vessels. There was no detectable difference in the intensity of labelling of basement membranes sandwiched between endothelial cells and subendothelial myocytes with basement membranes in the outer part of the vessel wall. The basement membranes of retinal cells that were in contact with blood vessels such as astrocytes, perivascular cells, glial cells, Müller cells were also labelled for type IV. In diseased vessels marked labelling surrounded activated myocytes but was largely absent from atrophic myocytes (Fig 2). Thickened basement membranes were evenly labelled with type IV, as were the multilayered basement membranes typical of hyalinised vessels (Fig 2). The inner half to three-quarters of hyalinised vessels contained type IV collagen, but the outermost region excluding the basement membranes of surrounding glial tissues was negative (Fig 2). It is noteworthy that the collagens in the outer half of the hyalinised vessel walls were identified as types I, III, V, and VI, and the distribution of types I and V in retinal vessels other than capillaries was identical to that of type IV, except that striated fibrils were also positive and that both collagen types were present throughout the entire thickness of hyalinised vessel walls.

Type III collagen was restricted to striated

*Figure 1: Retinal vessels in various stages of hyalinisation. (a) artery (A) and venule (V) of normal vasculature (category A). (b) hyalinised artery with thickening of vessel wall (category B). Some of the myocytes (arrowed) are atrophic. (c) grossly hyalinised artery (catergory C). Few myocytes are present and the vessel is surrounded by a thick layer of hyaline like material. (Toluidine blue, a×24; b×60; c×60.)*

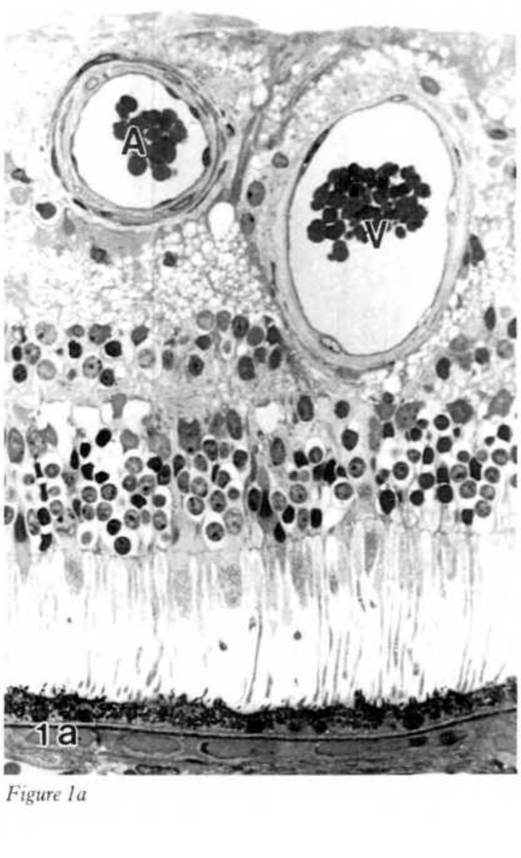

*Figure 1a*

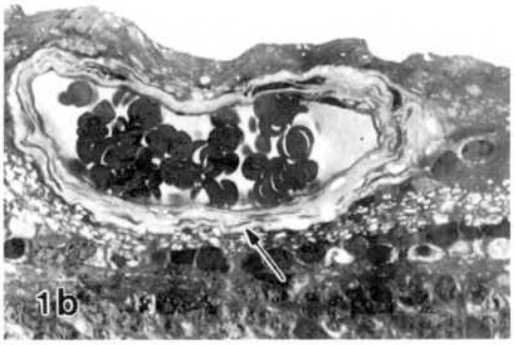

*Figure 1b*

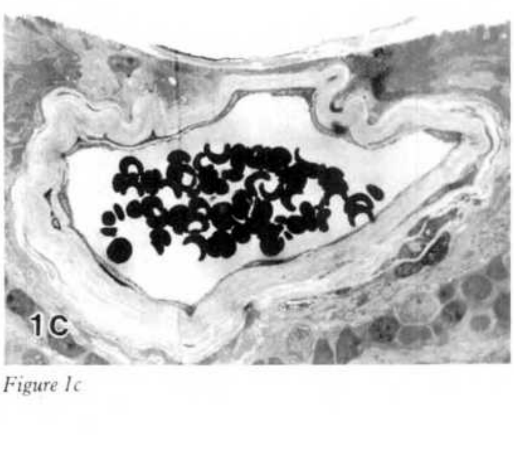

*Figure 1c*

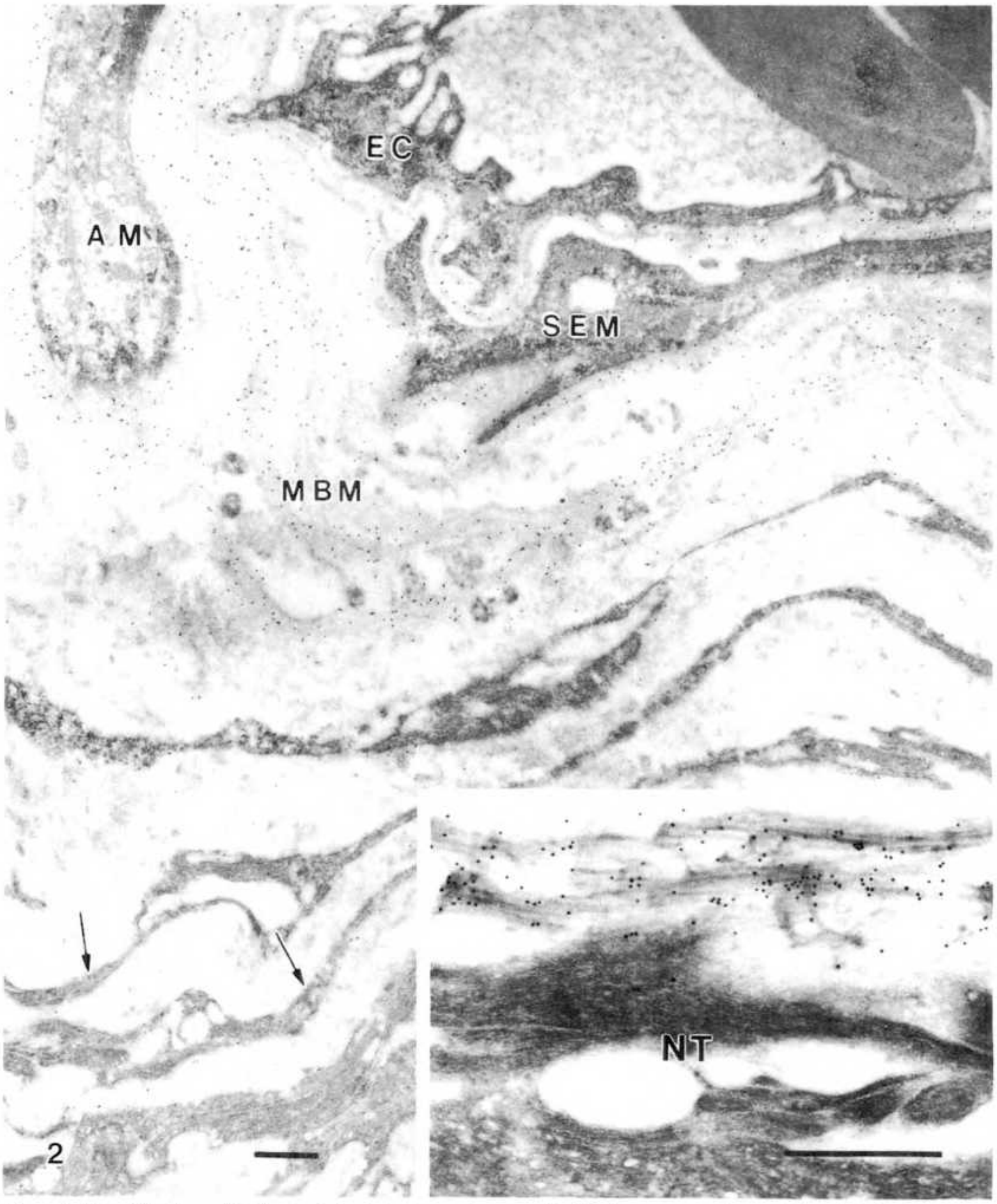

*Figure 2: Type IV collagen distribution in hyalinised artery (category B). The basement membrane of the endothelial cells (EC) and that of the subendothelial myocyte (SEM) are labelled for type IV collagen, as is the multilayered basement membrane (MBM) and an activated myocyte (AM). Atrophic myocytes are void of label (arrowed). (LR white, ×17 000, bar=0·5 μm.)*
*Insert: Labelling of striated fibrils at outer boundary of vessel wall with type III collagen antibodies. Neural tissue (NT) is free of label. (LR white, ×43 000, bar=0.5 μm.)*

collagen fibrils of large vessels (Fig 2), being completely absent from basement membranes. Type VI labelling was observed on striated fibrils (Fig 3) but was also noted in areas where striated fibrils were absent. Basement membranes sandwiched between endothelial cells and subendothelial myocytes were consistently negative for type VI as well as capillaries and small vessels. In larger vessels immunogold labelling for type VI was present on loose aggregations of collagen fibrils (Fig 3) but was largely absent over areas where the fibrils lay parallel to one another in tight bundles.

In capillaries labelling for type IV (Fig 2) was consistently stronger than that for type I (Fig 4), but there was no detectable difference in the pattern of distribution of the two collagen types. Endothelial cell basement membrane staining for types I and IV was not as intense as that on the outer side of intramural pericyte processes. There was no obvious increase in staining intensity with increasing endothelial cell or pericyte thickness. Capillaries in categories B and C contained a uniform distribution of both types I and IV throughout the width of the thickened basement membrane. Striated fibrils, more clearly visualised in ultrathin frozen sections, were absent.

## Discussion

A detailed search of the literature revealed the absence of studies concerning the fine structural localisation of collagen types in human retinal vessels. Moreover in animal studies such investigations of the retinal vasculature have been limited as to the collagen types examined. Cryoultramicrotomy has not been used in im-

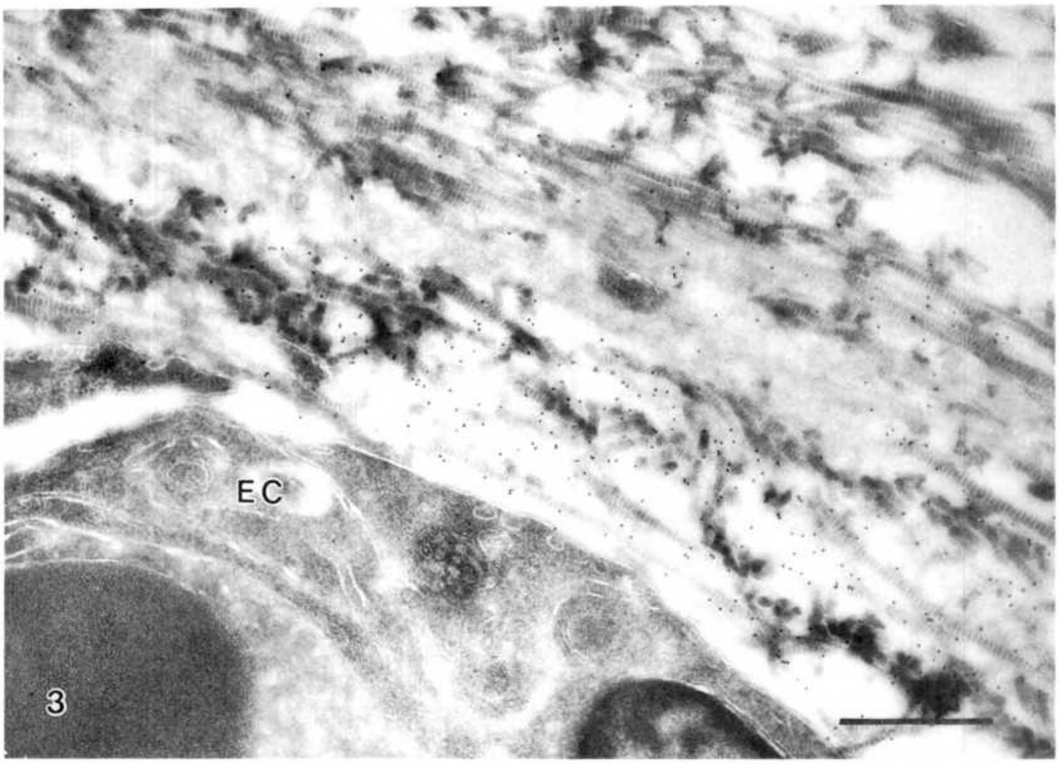

*Figure 3: Endothelial cell surrounded by loose aggregates of collagen fibrils labelling for type VI collagen. (Cryo, (44 000, bar=0·5 μm).)*

munocytochemical investigations of ocular disease, but we have found that with the use of this technique preservation of tissue antigenicity was more satisfactory than that of plastic embedding.

Collagens I, IV, and V have been localised by immunofluorescence in vessels of human,[7,8] bovine,[9] and rat[10] retinas. Jerdan and Glaser[8] found that a broad spectrum of retinal vessels stained for types I and IV, with types III and V primarily staining the walls of larger vessels.

Although immunofluorescence can be used to document the presence or absence of collagen types, the precise distribution within the retinal

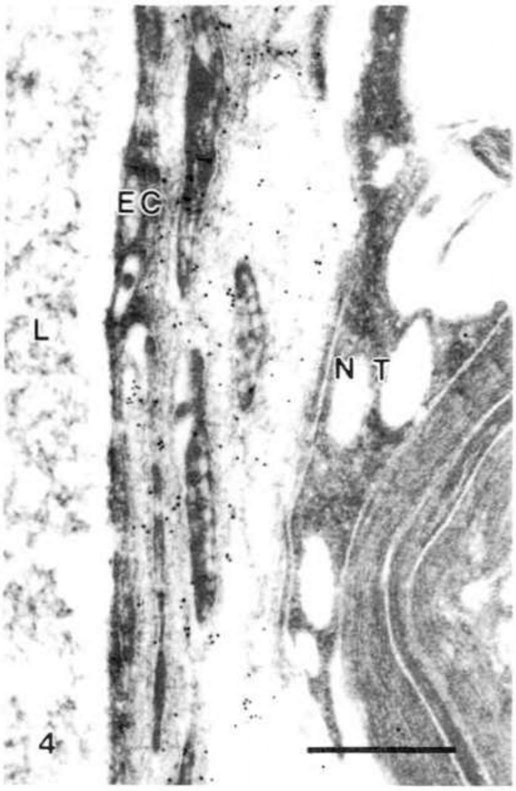

*Figure 4: Type I collagen labelling of basement membranes surrounding endothelial cell (EC) and myocytes. Note: vessel lumen (L), neural tissue (NT). (LR white, (×38 000, bar=0·5 μm).)*

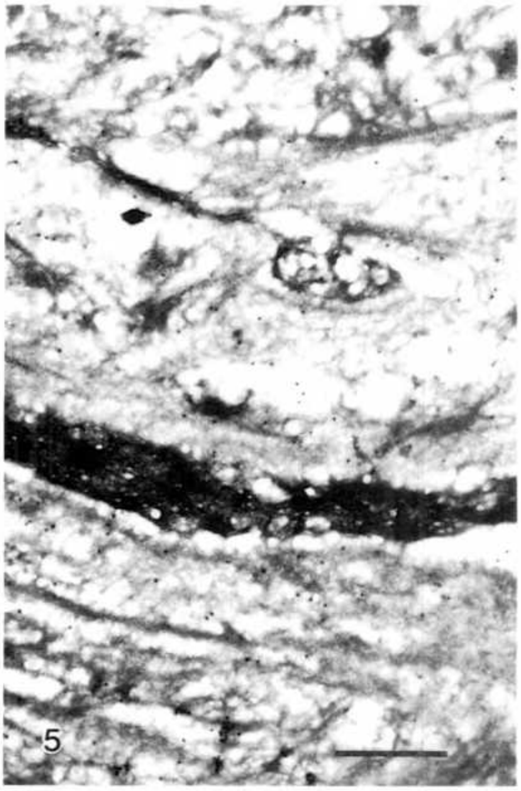

*Figure 5: Labelling of vessel wall for type V collagen. Both collagen fibrils and basement membrane are labelled. The tissue separation is attributed to cryo preparation. (Cryo, (×29 000, bar=0·5 μm).)*

vessel wall is elusive. Information on the ultrastructural distribution of collagen types, made available only through immunocytochemical electron microscopical studies, may be valuable in understanding such phenomena as matrix involvement in intramural neovascularisation. Manschot and Lee[3,4] have emphasised the frequency of neovascularisation within and around the walls of hyalinised blood vessels, and there is considerable evidence that changes in extracellular matrix components, including collagens, can have profound effects on endothelial cell behaviour. For example, type IV collagen was shown by Roberts and Forrester[11] to inhibit retinal vessel endothelial cell migration and proliferation in vitro, whereas type I collagen stimulated cell migration in vitro.

The advantage of fine structural localisation of the collagen types is underlined in the case of type IV collagen distribution in retinal capillaries. In our study type IV appeared to be more abundant on the outer basal lamina of the intramural pericytes than the basal lamina of the endothelial cells, an observation which could not have been made from the poor resolution immunofluorescent technology. This subtlety in type IV distribution was also noted by Essner and Lin[12] in rats but had been attributed to failure of antibody penetration. Our results confirm that this is in fact a difference in antigen concentration, since techniques employed in our study eliminate the problem of antibody penetration. This difference in antigen concentration may be extremely significant, since if pericytes produce more type IV collagen than endothelial cells, as this circumstantial evidence would indicate, then such a difference might be of significance in the proliferative stage of diabetic retinopathy. Pericyte loss is an early abnormality in diabetes, and this could presumably lead to a decrease in the amount of type IV collagen, thus removing the inhibiting influence that this collagen has on endothelial cell migration and proliferation.

In immunocytochemistry the use of imunogold is preferred to immunoperoxidase, since with the latter technique oxidised diamino benzidine (DAB) can diffuse from one site to another. This drawback can be illustrated by the report of Abrahamson,[13] who found that the localisation of laminin obtained with a post-embedding technique differed from that seen with the immunoperoxidase technique in glomerular basement membranes in which the label had diffused from the site of antigen location. Immunogold also lends itself to quantitation by image analysis, which has already been performed by other workers.[14] This may be important in the study of vascular disease, since the relative quantities of various collagen types are probably more significant than documentation of the actual types occurring in the area concerned.

In an immunomicroscope study of extracellular matrix of the monkey optic nerve head using LR white embedding combined with the immunogold technique, Morrison *et al*[15] noted the presence of types I, III, IV, and V within the walls of the central retinal artery with only the latter two labelling the basement membranes. Using antibodies supplied from the same source we noted that in addition to types IV and V, type I was also found to be present in the basement membranes of retinal vessels.

It is already known that basement membranes typically contain types IV and V collagen, with several workers demonstrating the presence of type IV in retinal microvessels.[8,16] The association of type I with basement membranes as seen in our studies was surprising, as interstitial collagen is not usually found in capillary basement membranes. Nevertheless microvessel preparations from rabbit cerebrum as well as bovine retinal microvessels have been shown to contain type I collagen.[16,17] On finding this collagen type in retinal vessels, including capillaries, Jerdan and Glaser[8] suggested that it is the presence of type I collagen that makes the human retinal vasculature so uniquely resistant to trypsin digestion. The extensive α-helical structure of type I collagen results in an increased stability to digestion by this protease.[18]

In the present study the fine structural distributions of collagen types I-VI have been documented in normal and aging retinal vessels. The technique of immunogold localisation appears to be of great value in future study of the changes which occur in the extracellular matrix components in ocular vascular disease.

This research was supported by a grant from the W H Ross Foundation (Scotland).

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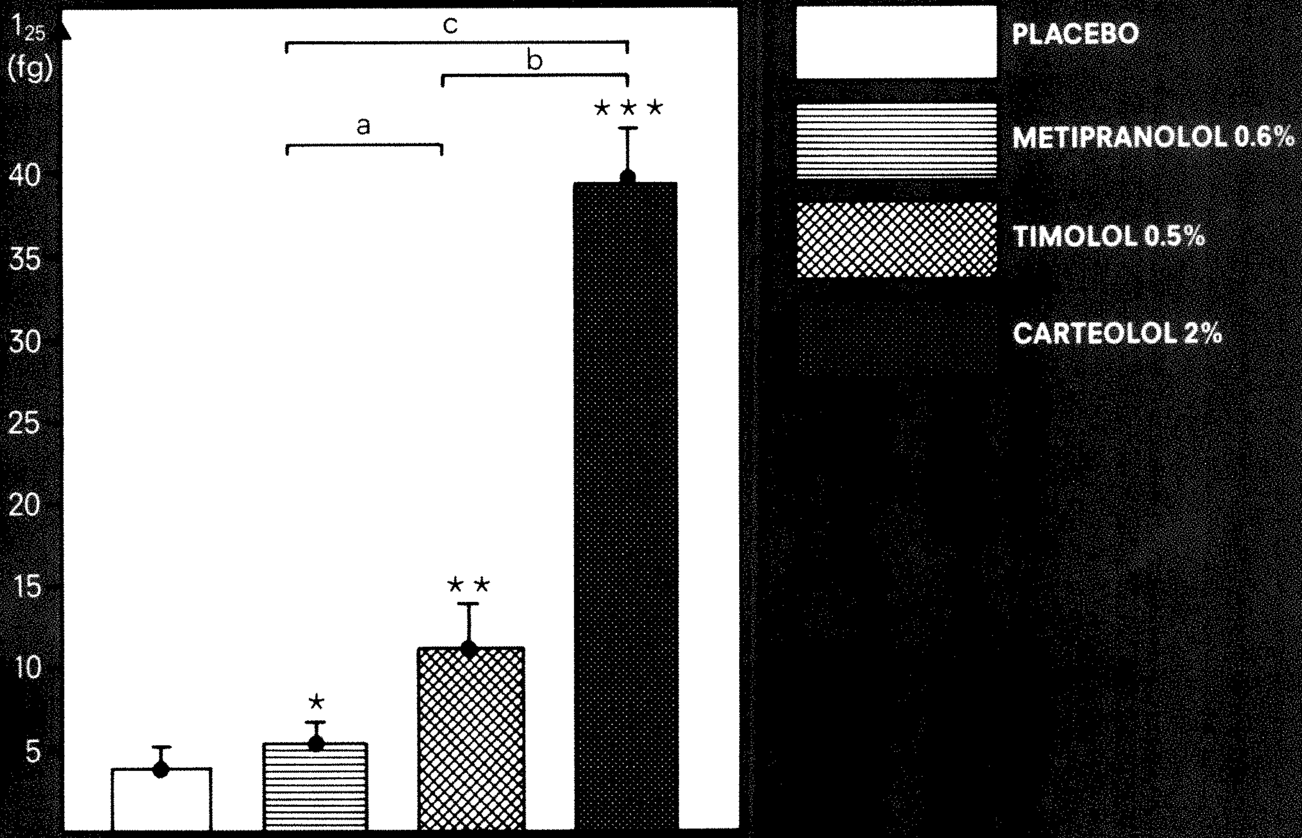

Dose of isoproterenol hydrochloride (mean ± SE) required to increase resting heart rate by 25 bpm ($I_{25}$) 3 hours after one drop of ophthalmic ß-blocker in each eye. ($^*P < 0.05$; $^{**}P < 0.001$; $^{***}P < 0.0005$ vs. placebo; a, $P < 0.02$; b, $P < 0.001$; c, $P < 0.001$.)

### (b) Exercise Tachycardia[2]

"Timolol significantly reduced exercise tachycardia ($P<0.05$) an effect which was not shown by metipranolol 0.1% or 0.3%."

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# Argon indirect ophthalmoscopic photocoagulation: reduced potential phototoxicity with a fixed safety filter

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## Abstract

**A new argon indirect ophthalmoscopic photocoagulator is presented which uses a red helium-neon laser aiming beam. An interference filter protects the operator from green or blue-green treatment beam reflections without impairing visualisation of the aiming beam or significant retinal anatomy. The protective filter is fixed in place, eliminating the weight, noise, and potential failure of mechanically switched filters. The red aiming beam has a negligible potential for producing photochemical retinal damage in the patient or operator.**

Binocular indirect ophthalmoscopic laser photocoagulation is useful for treating a variety of retinal disorders in the consulting room or operating room.[1] Previously described laser indirect ophthalmoscopes (LIOs) have used the same wavelength for aiming and treatment beams and either a switched or fixed protective filter system.

Switched protective filters remain out of the operator's view during fundus and aiming beam observation.[1,2] When the foot switch is depressed, they move into place, blocking treatment beam reflections. Switched filter systems provide unimpeded fundus observation, but they are heavy, noisy, and subject to mechanical failure, and the operator has no protection when viewing the aiming beam.

Fixed protective filter systems remain in place during observation and treatment.[3,4] Since they have no moving parts, fixed filters are silent and intrinsically reliable. When aiming and treatment beams are of the same wavelength, however, a fixed filter may reduce the intensity of the observable aiming beam to an unsatisfactory level. Increasing the intensity of the aiming beam is a poor solution to this problem because it increases the patient's risk of iatrogenic thermal or photochemical retinal damage.

Since there are problems with both switched and fixed protective filters when a single wavelength is used for LIO aiming and treatment beams, we have helped to develop a dual wavelength LIO with a red (632·8 nm) He-Ne laser aiming beam and a green (514·5 nm) or blue green (488 nm+514·5 nm) argon laser treatment beam.

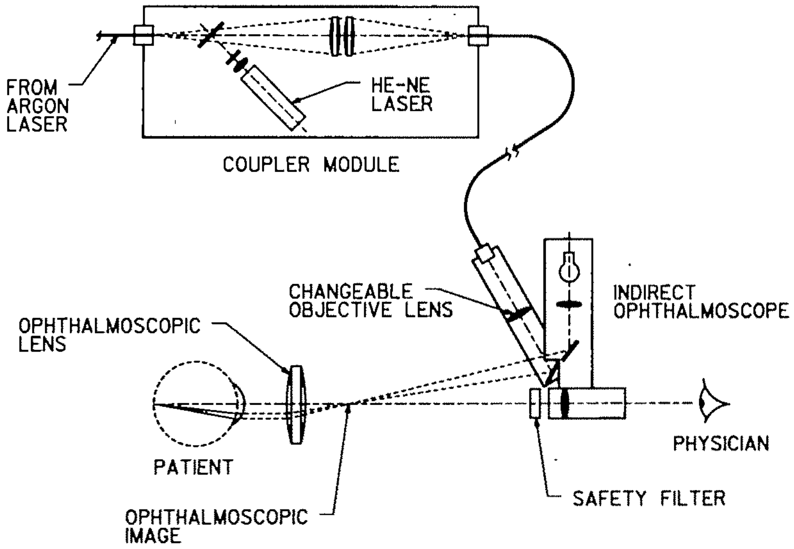

*Figure 1: The dual wavelength indirect ophthalmoscope photocoagulator consists of an argon laser console, a coupler module, and an indirect ophthalmoscope. A primary fibreoptic cable attaches the argon laser console to the coupler module, and a secondary fibreoptic cable attaches the module to the ophthalmoscope. The coupler module contains the ophthalmoscope's power supply and a 1 mW red He-Ne laser. The module combines the aiming and treatment beams into a single coaxial beam that is focused into the secondary fibreoptic cable. The coaxial beam exits the secondary fibre at the ophthalmoscope and is focused by a changeable objective lens before it reflects off a mirror. The operator directs the reflected beam into the patient's eye with a standard aspheric ophthalmoscopic lens. The user is protected from argon laser treatment beam reflections by an interference safety filter that blocks light between 455 nm and 525 nm but transmits light at shorter and longer wavelengths to permit effective ophthalmoscopy and visualisation of the red aiming beam.*

## Material and methods

An argon laser console (Coherent Medical Division, Model 920/930) is attached by a primary fibreoptic cable to a coupler module. The module is attached by a secondary fibreoptic cable to an indirect ophthalmoscope (Keeler Instruments, Fison model with modifications). The module contains the ophthalmoscope's power supply and a 1 mW red He-Ne laser. The optical system is illustrated in Figure 1.

The coupler module combines aiming and treatment beams into a single coaxial beam that is focused into the secondary fibreoptic cable. The coaxial beam leaves the secondary fibre at the ophthalmoscope and is focused by a changeable objective lens before it reflects off a mirror. The operator directs the reflected beam into the patient's eye using a conventional aspheric ophthalmoscopic lens.

The user is protected from argon laser treatment beam reflections by an interference safety filter that blocks light between 455 nm and 525 nm. The safety filter transmits light at shorter and longer wavelengths to permit effective ophthalmoscopy and visualisation of the red aiming beam. The He-Ne laser aiming beam is adjustable over a wide range of intensities for different viewing circumstances.

The aerial retinal image of an indirect ophthalmoscope is located anterior to the hand-held ophthalmoscopic lens, at a working distance from the operator determined by the power of the lens and the patient's eye. When the laser beam is focused precisely at that distance, retinal spot size is smallest and retinal irradiance is highest. The dual wavelength LIO produces a minimum retinal spot size of 320 μm with a 20-dioptre ophthalmoscopic lens. Since deviations as little as 50 mm from the focal plane of the ophthalmoscopic lens can double the spot size and reduce retinal irradiance by a factor of 4, changeable objective lenses (320 mm, 420 mm, and 520 mm focal lengths) are used to focus the laser beam at the proper working distance for different users. Deliberate deviation from the focal plane is a useful method of increasing retinal spot size.

## Results

The dual wavelength LIO has the same uses as those reported for single wavelength LIOs.[1,3,4] In the consulting room the LIO has been useful for panretinal photocoagulation through vitreous haemorrhage, for treating peripheral retinal breaks, for photocoagulation following vitreoretinal surgery requiring intraocular gas, and for treating patients whose frailty or obesity precludes conventional biomicroscopic photocoagulation. Additional operating room applications include photocoagulation in children under general anaesthesia and retinopexy after subretinal fluid drainage. With its built-in argon filters, the LIO can also be used to direct retinal endophotocoagulation when corneal or lenticular opacities preclude safe treatment with an argon laser beam originating outside the eye.[5]

The fixed safety filter gives the fundus a slightly yellowish tint but does not interfere with the detection of fundus details such as small retinal holes. The LIO is not useful for procedures such as macular photocoagulation that require precision in burn placement, because image magnification is too low and the patient's or operator's head may move. If motion is a problem in other procedures, decreasing the duration of exposure and increasing laser power can help limit size of burn, as can the use of repetitive mode photocoagulation, which provides a series of burns with a single depression of the foot switch.

## Discussion

Clinical infrared laser systems generally use a visible red He-Ne laser aiming beam.[6,7] Since infrared reflections can be blocked by a fixed safety filter that does not impair visualisation of the aiming beam or operating field, infrared laser safety systems are usually silent, lightweight, and intrinsically reliable. The safety system of the dual wavelength argon LIO has these same advantages. A similar system could be used with conventional biomicroscopic argon photocoagulators.

The dual wavelength LIOs red He-Ne laser aiming beam has the theoretical advantage of lower light scattering and better penetration of hazy ocular media than argon laser green or blue-green aiming beams.[8] It has another possible advantage unrelated to clinical applications. Experimental studies have shown that susceptibility to photic retinopathy increases with decreasing wavelength: ultraviolet and blue light have the greatest potential phototoxicity, while red light has negligible damage potential.[9-11] Studies have also shown that phototoxicity may be cumulative, so that light exposure increases the risk of damage to subsequent light exposure.[12]

In a conventional switched-filter LIO the user is unprotected when viewing argon blue-green or green aiming beam reflections. Furthermore, intense aiming beams are often needed for treating eyes with hazy ocular media. A recent study has demonstrated a subtle blue yellow colour contrast defect in long-term argon photocoagulator operators.[13] This defect is demonstrable only with extremely sensitive computerised testing, and its clinical significance is uncertain. If the defect is significant, however, the red aiming beam of the dual wavelength LIO system has an additional theoretical advantage: negligible potential retinal phototoxicity for the patient and operator.[8,11]

This research was supported in part by the Kansas Lions Sight Foundation, Inc. and Research to Prevent Blindness, Inc. M M Whitacre and M A Mainster do not have a proprietary interest in any indirect ophthalmoscope, laser system, or manufacturer. N Manoukian is an employee of Coherent Medical Division which produces ophthalmic laser systems.

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British Journal of Ophthalmology, 1990, 74, 235–237

# Diagnostic value of 'optic foramen views': experience from an eye hospital

Ivan Moseley

## Abstract

**A prospective survey of 174 consecutive patients in whom plain radiographs of the optic canals were requested by ophthalmologists disclosed no cases in which these films made a positive contribution to management. It is suggested that as a general rule this radiographic examination has no useful role.**

Conventional radiographs of the optic canals, popularly referred to as 'optic foramen views,' require skilled radiography and interpretation, are time consuming, and involve a small but unavoidable dose of radiation to the lenses of the eyes. Furthermore, it can be argued that in most cases they contribute little, if at all, to management. They have been almost totally abandoned by neurologists and neurosurgeons[1] but not by ophthalmologists, whose recourse to computed tomography, for example, may be less ready. The present study was designed to establish when, or if, they are indicated.

TABLE I *Optic foramen views: indications and findings*

| *Indication* | *Number* | *Findings* | | | |
|---|---|---|---|---|---|
| | | *Normal* | *Abnormal* | *Equivocal* | *Unknown* |
| Visual disturbance | 124 | 119 | 4 | 1 | |
| Proptosis/orbital mass | 20 | 16 | 2 | | 2* |
| Orbital pain/headache | 10 | 10 | | | |
| Swollen or cupped discs | 7 | 7 | | | |
| Eye movement disorder | 7 | 7 | | | |
| Unknown | 3* | 1* | | | 2* |
| Trauma | 1 | | 1 | | |
| Epilepsy | 1 | | 1 | | |
| Neurofibromatosis | 1 | 1 | | | |
| Total | 174 | 162(93·5%) | 7(4%) | 1(0·5%) | 4(2%) |

* Documents unavailable.

TABLE II *Abnormalities on optic foramen views in 7 cases*

| *Indication* | *Abnormality* | *Findings on other studies* |
|---|---|---|
| Visual loss | Air in globe | Skull: air in globe |
| Optic atrophy | Ipsilateral superior orbital fissure large | Skull: superior orbital fissure large |
| Blurred vision | Both canals enlarged | Skull and CT: empty sella |
| Optic disc hypoplasia | Ipsilateral canal small | |
| Trauma | Ethmoid fracture | Skull: ethmoid blowout |
| Optic nerve glioma | Ipsilateral canal large | CT, MRI: glioma, large canal |
| Orbital mass | Frontal sinus mucocele | Skull: frontal sinus mucocele |

## Material and methods

As part of a wider prospective survey a record was kept of the indications and findings in patients referred to the radiology department for 'optic foramen views' between January and December 1988. No specific radiological control was exercised on referrals during that time. The findings were those of a consultant ophthalmic radiologist or, in about 10% of cases, of one of two neuroradiological senior registrars. A record was also kept of the findings on any other imaging procedure (other than orbital sonography) to which these patients were subjected during the review period.

## Results

Plain films of the optic canals were requested for 174 patients, for all but three of whom skull films were also obtained. The indications for and the findings on the optic foramen views are shown in Table I.

There were seven cases in which the optic canal views were thought to be abnormal (Table II). One of these was a child known for many years to have a glioma of the optic nerve in whom CT had shown the tumour to extend into the optic canal (Fig 1), and in another child a small optic canal on the affected side was associated with optic disc hypoplasia (Fig 2). In a young woman with an episode of blurred vision and normal optic discs bilateral enlargement of the optic canals was thought possibly to be the consequence of dilatation of the optic nerve sheaths, indicating chronic increase in intracranial pressure. No clue to aetiology was given by the plain films, though CT showed an empty sella turcica (Fig 3).

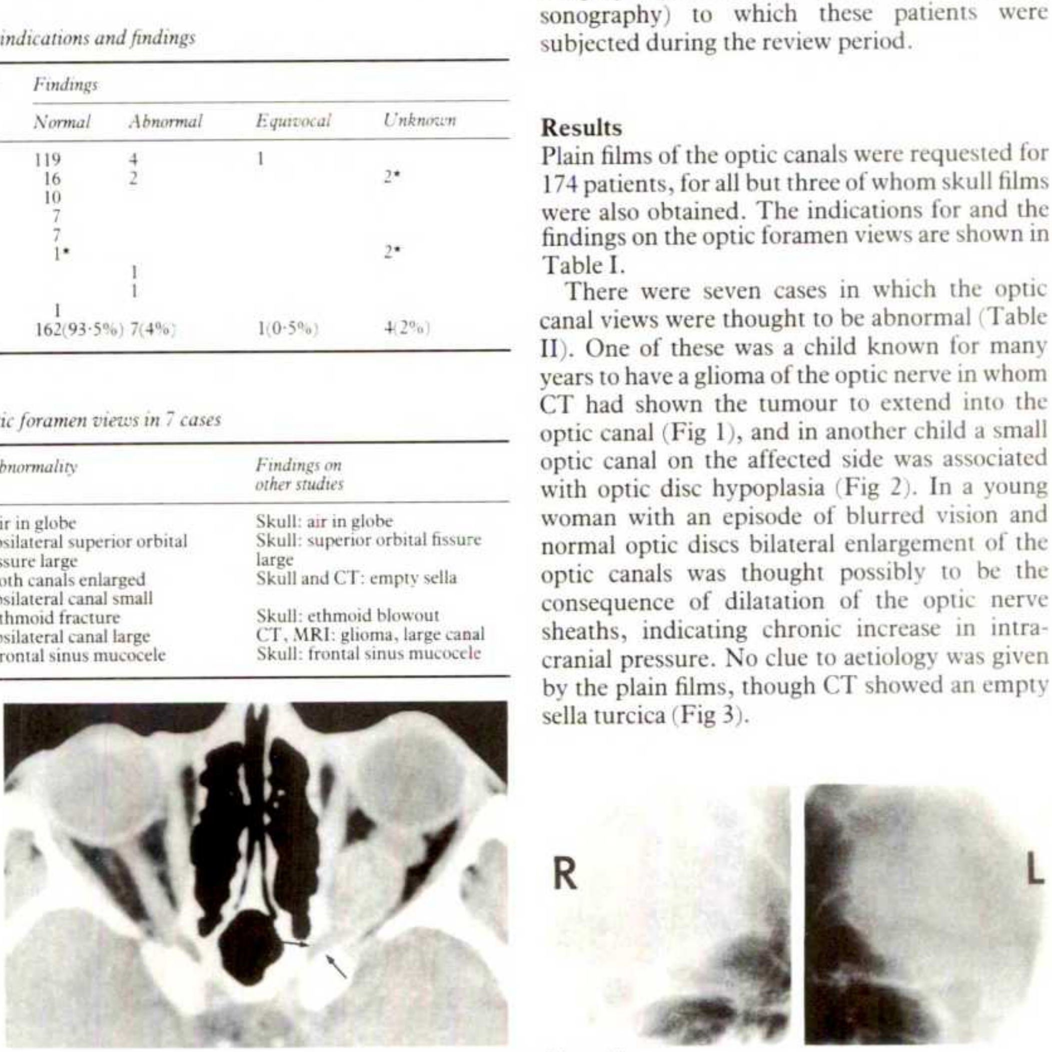

*Figure 1a*

*Figure 1b*

*Figure 1: A girl aged 15, diagnosed some years previously as having a glioma of the left optic nerve. (a) Contrast-enhanced axial CT showed the large retrobulbar tumour funnelling down into the enlarged left optic canal (arrows). (b) Optic canal views performed on a subsequent visit again demonstrated the enlargement of the left canal.*

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The abnormality visible on the coned views in the remaining patients did not affect the optic canals and was also evident on the skull radiographs. In six patients with visual disturbance and in two with intraorbital mass lesions the skull radiograph and/or other tests were abnormal, while the optic foramen views were interpreted as normal. CT was carried out in one patient because of erroneous interpretation of the optic foramen views by an ophthalmologist. It confirmed the normality of the plain films reported by the radiologist. Questionable findings reported in one further case were not confirmed by subsequent investigations.

There were thus no cases in which abnormalities shown by the optic canal radiographs, not evident clinically or on other simple imaging tests, contributed positively to patient management.

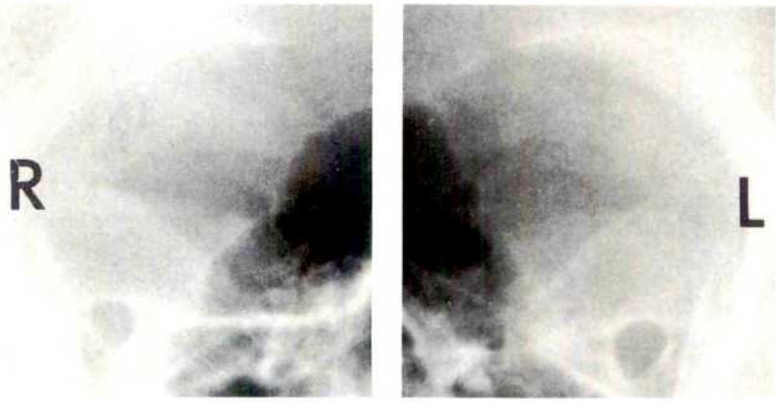

*Figure 2: A 3-year-old boy was noted to have poor vision in the right eye, but funduscopy, performed with suboptimal co-operation, was thought to be normal. The optic canal views showed the left side to be normal, while the right canal was small. Further examination by a paediatric neuro-ophthalmologist, unaware of the radiographic findings, revealed a hypoplastic optic disc on the right.*

## Discussion

'Careful study of routine skull *x*-rays and optic canal views may yield vital diagnostic information (in patients with optic nerve compression) and

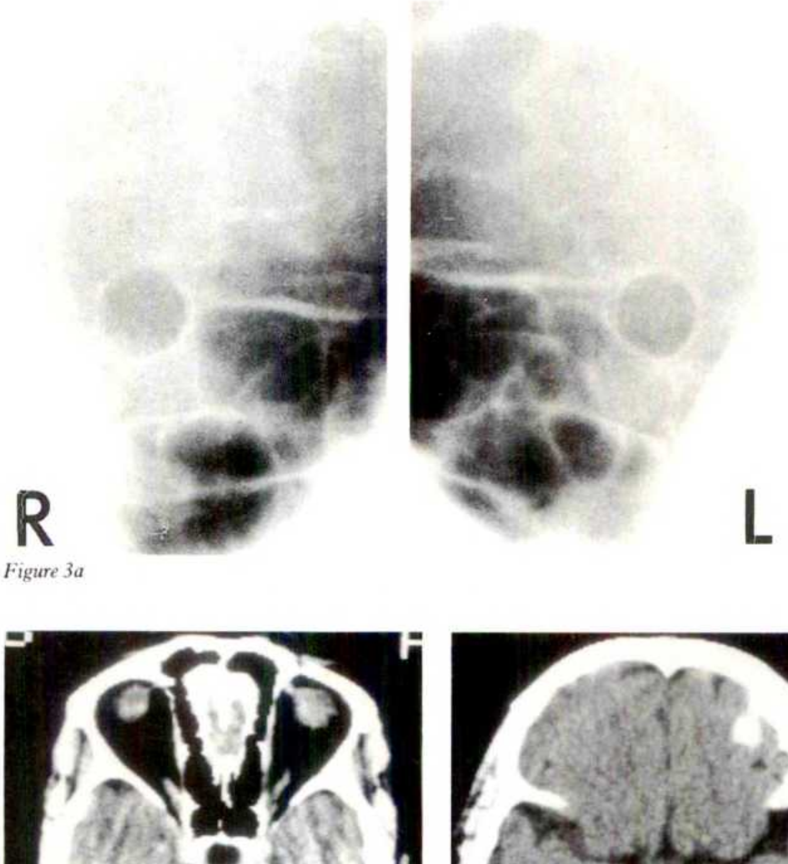

*Figure 3a*

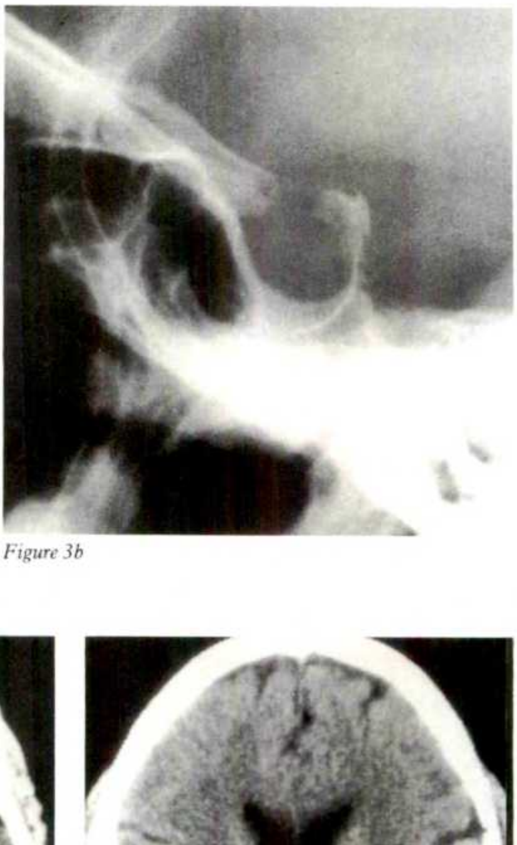

*Figure 3b*

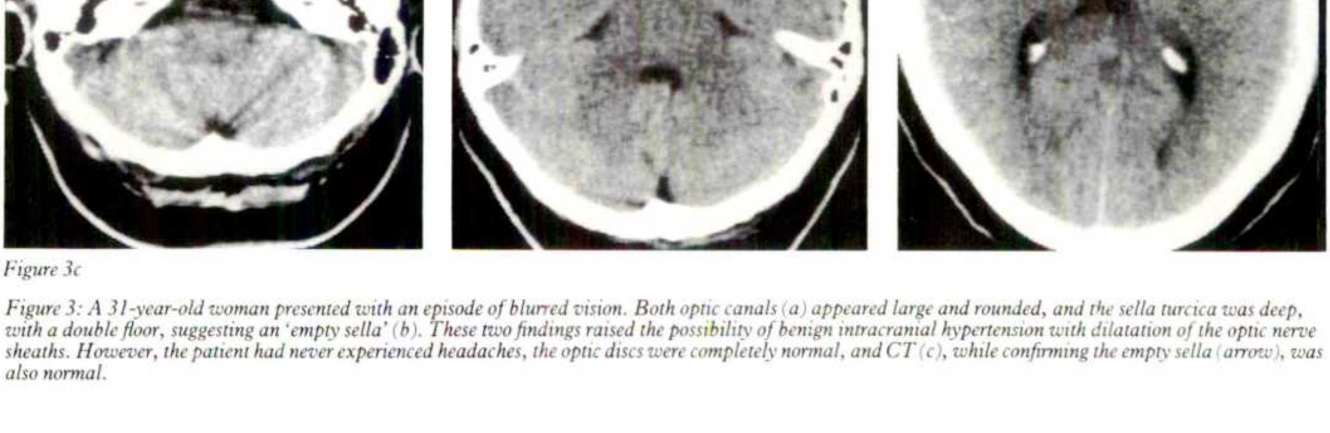

*Figure 3c*

*Figure 3: A 31-year-old woman presented with an episode of blurred vision. Both optic canals (a) appeared large and rounded, and the sella turcica was deep, with a double floor, suggesting an 'empty sella' (b). These two findings raised the possibility of benign intracranial hypertension with dilatation of the optic nerve sheaths. However, the patient had never experienced headaches, the optic discs were completely normal, and CT (c), while confirming the empty sella (arrow), was also normal.*

should under no circumstances be omitted'.[2] With improvements in the quality and availability of CT and the introduction of magnetic resonance imaging (MRI) this view has been overtaken by history, and in neurological practice plain films are used with ever decreasing frequency.[1,3]

Unlike skull or chest radiographs, optic foramen views have no useful screening role: they are specifically designed to show, with minimal distortion, changes in size or shape of the optic canals or in the density or texture of the surrounding bone, and are indicated, if at all, in the assessment of unilateral optic neuropathy.[4] Thus, while patients with orbital pain, headache, bilateral papilloedema, eye movement problems, and even epilepsy account for less than 15% of those referred for optic foramen views in the present series, these referrals would appear to have no anatomical or physiological basis. Similarly, adults with proptosis or palpable orbital masses in whom vision is not severely affected (12 cases in the present series) are unlikely to benefit from radiography of the optic canals.

Orbital CT is very rarely positive in patients with unilateral visual loss and no other signs of an orbital mass lesion.[5] Moreover, visual loss due to lesions confined to the optic canal, without orbital involvement, is inordinately rare.[6] In the present series there were more cases in which a significant lesion was not shown by the optic foramen views than true positives, but these cannot reasonably be classified as false negatives, since the examination failed to show abnormalities for which it was not designed.

A patient with unexplained visual loss requires a definitive examination such as CT or MRI. Since plain films are normal more often than not in patients with orbital meningiomas,[7] so that neither positive nor negative results on optic foramen views should obviate further imaging investigations, the plain films can be dispensed with entirely, without prejudice to the patient.

It may be argued that in children with optic pathway gliomas plain radiography is a simple way of assessing enlargement of the intracanalicular portion of the optic nerve, but in cases in which this information will modify management MRI is probably more sensitive. In the group reviewed here only two of the patients (one of whom did not have visual symptoms) were under 10 years old, and there were a further six aged under 20.

The radiation dose from adequate optic foramen views is of the order of 1–2 cGy, but repeat exposures are not uncommon, and since skull films are usually requested at the same time the effective dose to the lens from the latter examination (2 cGy)[8] might often be more than doubled. There is no reason to suppose that the series of consecutive patients involved in this prospective study are in any way exceptional, and the conclusion that there is no role for diagnostic optic foramen views would seem inescapable.

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## MINI REVIEW

# New light on visual pigment genes

The recent explosion in knowledge about the human genome, resulting from the application of the new methods of molecular genetics, has extended to our understanding of the genes encoding visual pigments. This in turn has given us new insight into the mechanisms of normal and abnormal colour vision as well as basic mechanisms of evolution.

Visual pigments, which reside in the plasma and disc membranes of photoreceptor outer segments, consist of an apoprotein, opsin, covalently linked to 11-cis-retinal, the apoprotein in each visual pigment being encoded by a different gene. The absorption of a photon by a visual pigment results in the isomerisation of retinal from the 11-cis to the all-trans configuration, and this ultimately results in the production of a neural signal.

Recent work by Nathans and his colleagues[1,2] started with the assumption that the rod pigment, rhodopsin, and the cone pigments all evolved from a common ancestor and, as a result, would contain similar sequences of nucleotides. Using a bovine rhodopsin gene as a probe, they found that it bound strongly to one segment of human DNA and less strongly to three other DNA segments. The segment to which the bovine rhodopsin gene bound strongly was shown to be the gene encoding human rhodopsin which resides on chromosome 3.[3,4] The three segments to which it bound less strongly were shown to be the genes encoding the colour vision pigments, two (the red and the green colour vision genes) being on the X chromosome and one (the blue colour vision gene) on chromosome 7.[2] Bovine and human rhodopsin are approximately 90% identical in DNA sequence,[5,6] human rhodopsin and colour pigments are approximately 40% identical,[6] while the red and green pigments show only 43% identity with the blue pigment but 96% mutual identity.[1] The fact that the genes encoding the red and green pigments are 96% identical and are located at the end of the long arm of the X chromosome suggests that they arose by an evolutionarily recent duplication event.

One unexpected finding was that, while males with normal colour vision have one red pigment gene on each X chromosome, the number of green pigment genes varied from one to three,[1] while occasionally there may even be four or more green pigment genes.[7]

Nathans and his colleagues then studied people with the four classes of red and green colour blindness. People with deuteranopia were found to have a normal red pigment gene but no green pigment gene(s). Those with protanopia lacked a normal red pigment gene, which was replaced by a hybrid red-green pigment gene, and they had no green pigment gene or a variable number of them. Deuteranomalous trichromats had a normal red pigment gene, a hybrid red-green gene, with or without normal gene pigment genes. Protanomalous trichromats had no normal red pigment gene, a hybrid red-green pigment gene, and a variable number of green pigment genes. These findings were explained by unequal crossovers that resulted in the deletion of a pigment gene or the production of different fusion genes consisting of varying portions of the red and green pigment genes.[2,8] People with protanopia and protanomaly appear to have the same genotype (one red-green fusion gene and one intact green gene). These phenotypic differences could be due to slight differences in the crossover points between the red and green pigment genes, resulting in protein pigments with different in-vivo light sensitivity, causing different colour perception.[9] Similarly, differences in crossover points could explain the variations that have been described in the degree of impairment in people with anomalous trichromacy (protanomaly and deuteranomaly). The molecular methods used up to the present cannot distinguish between small differences in the position of crossover points.

It is interesting that the gene for X-linked blue cone monochromatism maps to Xq28, the site of the red and green pigment genes. It is possible that this rare disorder, characterised by poor vision, nystagmus, photophobia, and achromatopsia, results from alteration of these two pigment genes so that they do not function, or from their deletion.[10]

The observation that humans and Old World monkeys have red and green pigment genes on their X chromosome while New World monkeys have one long wavelength gene on their X chromosome[11] has led to the suggestion that short wavelength (blue), long wavelength (red and green), and rod pigments all diverged from a common ancestor more than 500 million years ago, and that the red and green pigment genes were generated, after a duplication event, after the split between New and Old World primates some 30 to 40 million years ago.[1] An alternative suggestion is that the rhodopsin gene and the common ancestor of the colour pigment genes diverged first, about 800 million years ago, and that the three different colour pigment genes evolved after that.[12]

There is still much to learn about visual pigments, many questions about colour vision that remain unanswered, but already the new genetics has produced exciting avenues for further study.

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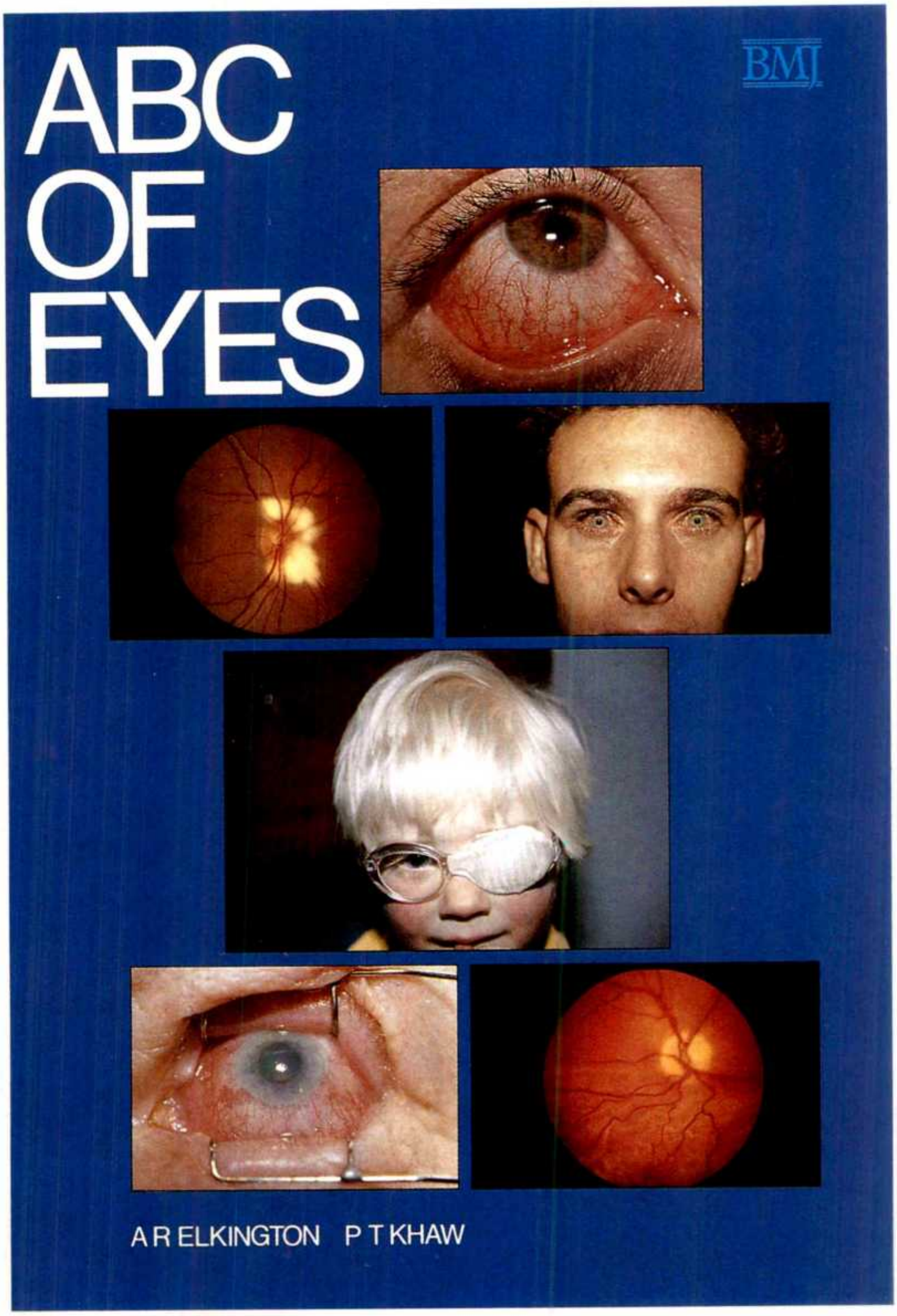

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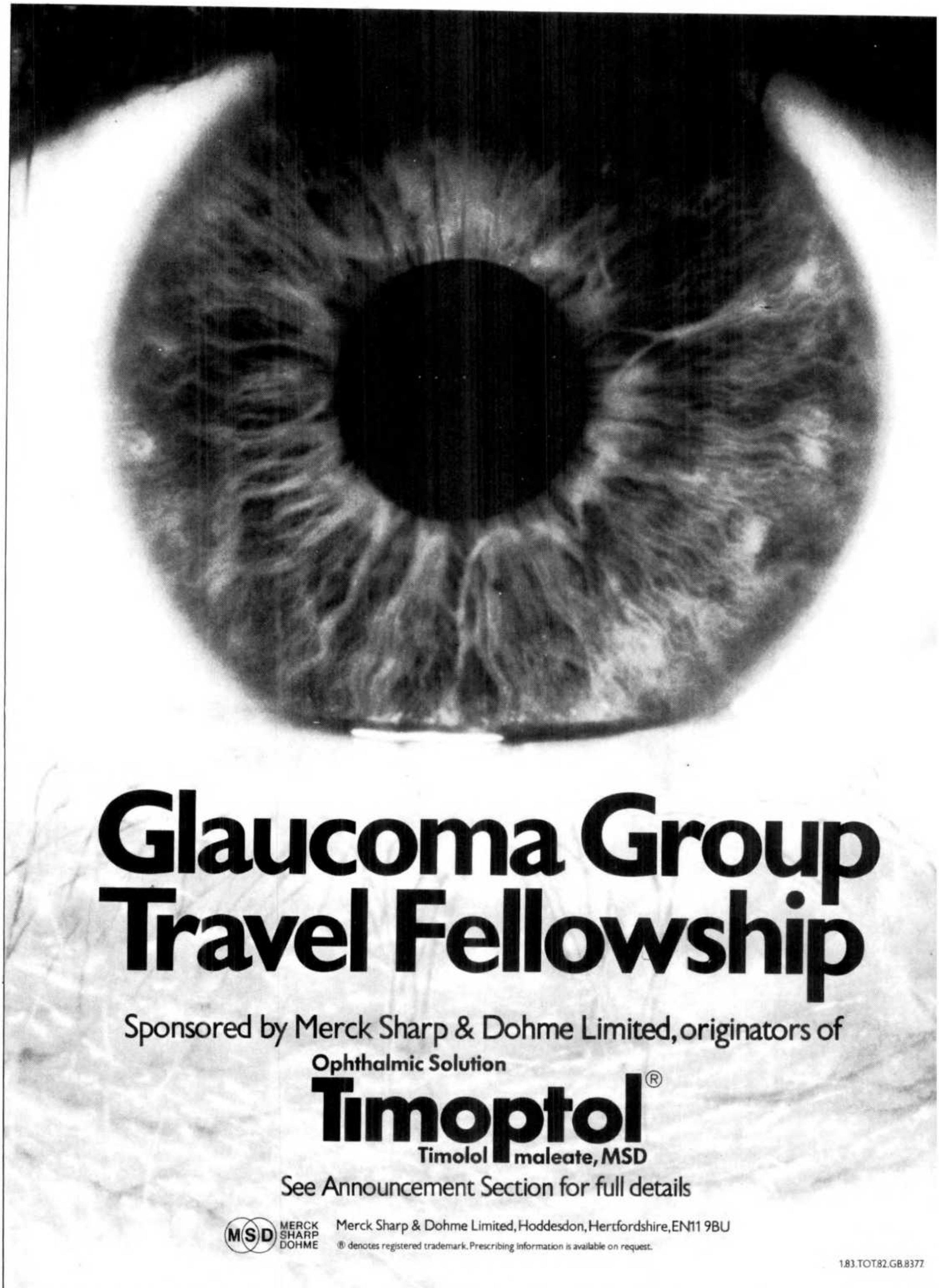

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CASE REPORTS

# Bilateral failure of adduction following orbital decompression

F Kinsella, P Kyle, A Stansfield

**Abstract**

**We report a case of bilateral complete failure of adduction following bilateral translid antral-ethmoidal orbital decompression. We believe the probable mechanism is neuropraxia (temporary dysfunction) of the third cranial nerves' supply to the medial recti, owing to these nerves' occupying an anatomically abnormal position. Partial recovery of adduction occurred over the ensuing six months.**

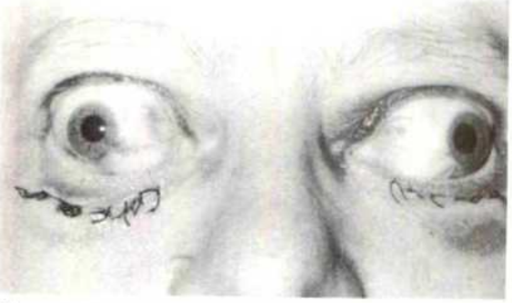

*Figure 1: Both eyes divergent in the primary position on the first postoperative day.*

In 1975 a 34-year-old woman in whom thyrotoxicosis and pretibial myxoedema had very recently been diagnosed was referred by the endocrinological service to our department for ophthalmological assessment. Examination at that time showed her best vision was 6/9 in both eyes (with a −2·0 sphere and +5·50×80° in both eyes). Bilateral exophthalmos was present, the Hertel exophthalmometer measuring 23 mm on the right and 21 mm on the left side. Moderate lid lag and retraction were noted. A mild degree of lagophthalmos was present bilaterally, but corneal examination showed a normal appearance. Pupillary and fundal assessment gave normal results, as did measurement of intraocular tensions. The patient showed absence of convergence, but otherwise ocular movements were full.

Over the succeeding 11 years our patient's ocular status remained remarkably stable, her only symptoms being occasional grittiness. In 1987, however, her disease became much more active, with the appearance of marked congestion over the insertions of the horizontal recti and oedema of the caruncles. Corrected visual acuity fell to 6/18 bilaterally, and slight swelling of both optic discs became apparent. The degree of exophthalmos, however, remained static, and at no stage was there evidence of exposure keratitis. A CT scan of the orbits showed signs consistent with compressive neuropathy, and, because of her failing to respond to high-dosage systemic steroids, bilateral translid antral-ethmoidal decompressions were performed in August 1987.

The surgical procedure was uncomplicated, but it was noted at the time of surgery that the anterior ethmoidal arteries were located far more antero-inferiorly than normal.

On the day after surgery the patient's vision had improved to 6/12 in the right and to 6/9 in the left eye, but a marked divergent squint in the primary position was present (Fig 1). Examination of ocular movements revealed bilateral failure of adduction, the right eye being unable to reach the midline (Fig 2A) but reaching the midline on the left side (Fig 2B). The patient's other eye movements were normal. Forced duction testing demonstrated limitation of adduction in the right eye only on extreme adduction, whereas the left eye showed no limitation of adduction whatsoever. Force generation testing (whereby the patient performs ocular movements on command while the surgeon grasps the insertion of the appropriate

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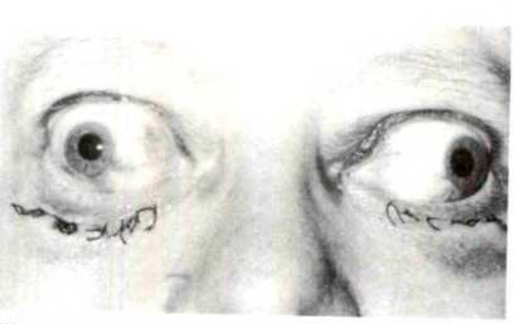

*Figure 2A: Left lateral gaze immediately after operation, demonstrating inability of the right eye to reach the midline.*

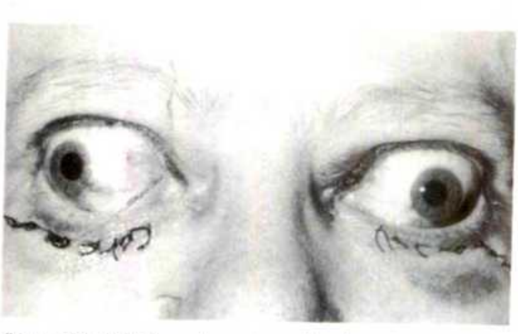

*Figure 2B: Right lateral gaze immediately after operation, demonstrating partial adduction of the left eye.*

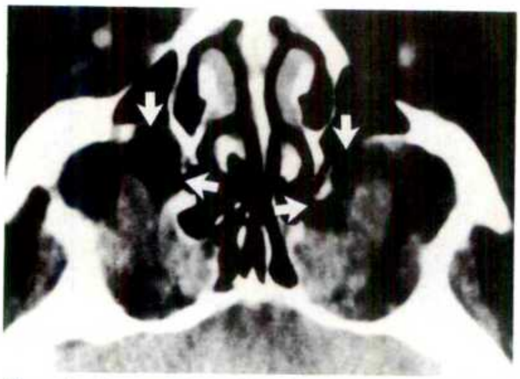

*Figure 3A: Postoperative orbital CT scan showing evidence of antral-ethmoidal decompressions (arrows) as well as enlarged extraocular muscles consistent with Graves' ophthalmopathy.*

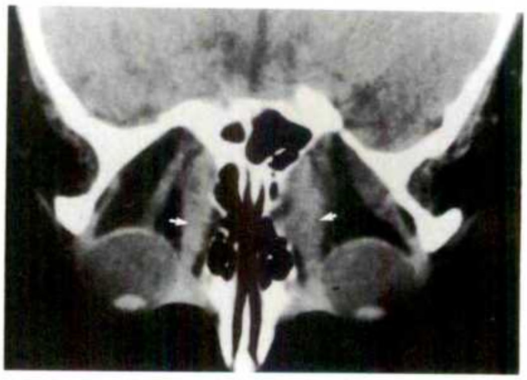

*Figure 3B: Postoperative orbital CT scan demonstrating that there has been no avulsion or disinsertion of the medial recti muscles (arrows).*

rectus muscle) showed that active adduction from the abducted position was entirely absent in the left eye, and, though present in the right eye, its force was markedly diminished. A repeat orbital CT scan, apart from demonstrating signs of the bilateral floor and medial wall decompressions, showed that the recti muscles were essentially unchanged in appearance: in particular there was no evidence of avulsion or disinsertion of the medial recti (Figs 3A, 3B).

A trial of high-dosage systemic steroids failed to produce any improvement in ocular motility and was consequently discontinued after one week. Over the succeeding months, however, the patient's adduction began to improve spontaneously, so that six months after surgery some recovery of adduction had occurred bilaterally (Figs 4A, B). In addition the patient's convergence – which had not been present since first assessed in 1975 – had shown a certain amount of recovery (Fig 5).

At present (two years after surgery) our patient's ocular motility has shown considerable improvement. There has been significant recovery of adduction bilaterally, some convergence is present, and there is only 5° of left divergence in the primary position (Fig 6).

## Discussion

Muscle imbalance following orbital decompression is well recognised,[1-5] but apart from the Naffziger[6] anterior cranial fossa approach, which may be complicated by damage to the superior orbital fissure structures[7] (resulting in third, fourth, or sixth cranial nerve pareses), the mechanism is almost invariably a mechanical disturbance of the extraocular muscles. The risk of muscle imbalance depends on the particular procedure performed, being a frequent complication of three wall (36% in the series of Harting F, *et al*[5]) and transantral antral-ethmoidal (33-41%),[2 3 5] but rarely following translid antral-ethmoidal decompression (5·6%).[4] The much higher incidence of motility disturbance following transantral rather than translid antral-ethmoidal decompressions is thought by some to be related to a more posterior decompression being achieved with the former approach, causing loss of support for the muscle cone at the orbital apex,[4] though lack of direct visualisation with the former approach may contribute somewhat to this higher incidence. The occurrence of an A-pattern of motility disturbance in eight out of a series of 14 patients following anterior ethmoidal orbital decompression has recently been reported,[7] the postulated cause being selective disruption of orbital fascial septa by the relieving periosteal incisions.

We believe that our patient's bilateral failure of adduction was due to neuropraxia (temporary dysfunction) of the third cranial nerves' supply to the medial recti for the following reasons: force generation testing demonstrated an inability to adduct the eyes on command, forced duction testing failed to show any significant mechanical restriction, while inadvertent avulsion of the medial recti was excluded by CT scanning. Additional evidence of neuropraxia is that some recovery of adduction occurred over a six-month period. So far as we are aware this is the first documented case of bilateral isolated adduction failure following orbital decompression.

As the medial recti are normally innervated from the global aspect, trauma to these nerves

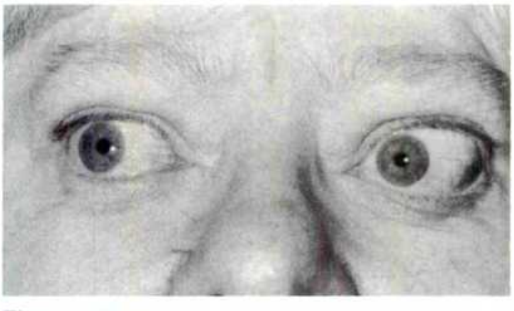

*Figure 4A: Right lateral gaze six months postoperatively demonstrating some recovery of left adduction.*

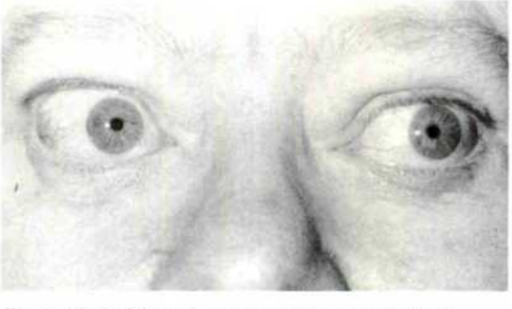

*Figure 4B: Left lateral gaze six months postoperatively demonstrating some recovery of right adduction.*

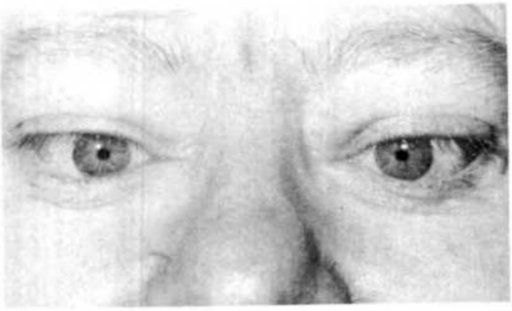

*Figure 5: Some recovery of convergence six months postoperatively.*

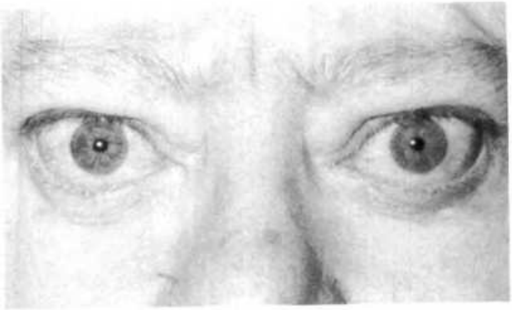

*Figure 6: Recent photograph showing the eyes in the primary position. The corneal reflexes are asymmetrical, and the cover test reveals that 5° of left divergence is present.*

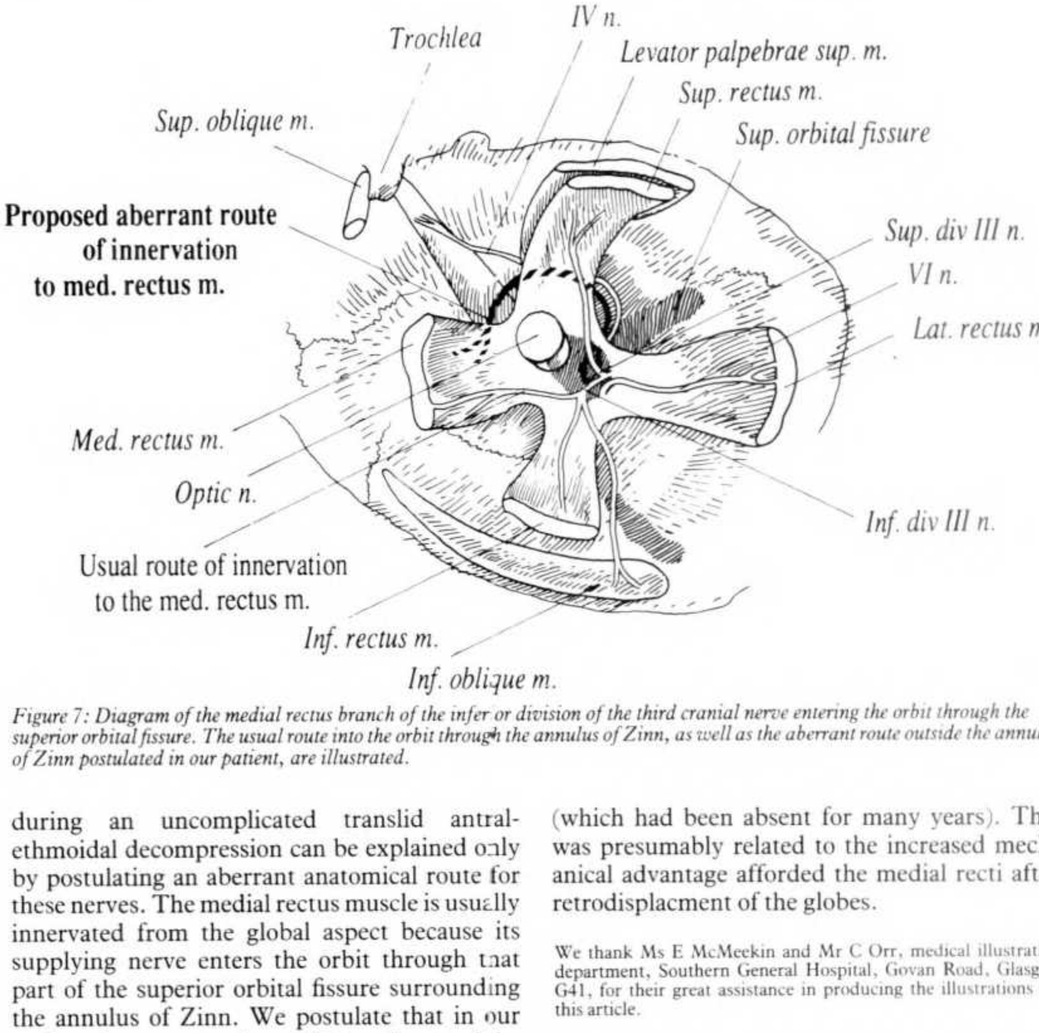

*Figure 7: Diagram of the medial rectus branch of the inferior division of the third cranial nerve entering the orbit through the superior orbital fissure. The usual route into the orbit through the annulus of Zinn, as well as the aberrant route outside the annulus of Zinn postulated in our patient, are illustrated.*

during an uncomplicated translid antral-ethmoidal decompression can be explained only by postulating an aberrant anatomical route for these nerves. The medial rectus muscle is usually innervated from the global aspect because its supplying nerve enters the orbit through that part of the superior orbital fissure surrounding the annulus of Zinn. We postulate that in our patient the nerves to the medial recti entered the superior orbital fissures outside the annulus of Zinn (as does the trochlear nerve), thus gaining access to the orbital aspect of the medial recti muscles (Fig 7), where it was injured during surgery. This theory is supported by the symmetry of the lesions produced on both sides and the peroperative observation that the anterior ethmoidal arteries occupied an abnormal position in the orbits.

A surprising outcome was partial recovery postoperatively of the patient's convergence (which had been absent for many years). This was presumably related to the increased mechanical advantage afforded the medial recti after retrodisplacment of the globes.

We thank Ms E McMeekin and Mr C Orr, medical illustration department, Southern General Hospital, Govan Road, Glasgow G41, for their great assistance in producing the illustrations for this article.

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*British Journal of Ophthalmology*, 1990, **74**, 242

# Orbital haemorrage induced by labour

Orna Geyer, Daniel Wasserman, Leonard Rothkoff, Moshe Lazar

## Abstract

**A case of acute orbital haemorrhage induced by labour is reported in a woman giving birth for the eighth time. The diagnosis was confirmed by computed tomography. The haemorrhage subsided spontaneously within three weeks. The mechanism of orbital haemorrhage following certain kinds of strain is discussed.**

Orbital haemorrhage (OH) is usually associated with factors such as trauma and venous anomalies,[1] less frequently with strain.[2] Induced by labour it has been reported only once.[3] We present an additional case confirmed by computed tomography.

## Case report

A 38-year-old woman was referred to us by her gynecologist because of proptosis of the left eye which was noticed immediately after labour. The patient was otherwise well. This was the patient's eighth labour, and she gave a history of exophthalmos, which subsided spontaneously within three weeks, following the fifth and sixth deliveries.

Her corrected visual acuity was 6/6 in both eyes. A general ocular examination of the left eye showed slight ptosis of the eyelids. conjunctival chemosis, and an irreducible proptosis of 4 mm (by Hertel measurement) in comparison with the right eye. Limitation of adduction and abduction was also noted.

A computed tomography (CT) scan (Fig 1) revealed a mass located in the lateral part of the left orbit that pushed the eyeball forward. The image of the lesion was more attentuated than that of the surrounding soft tissue and was therefore interpreted as haemorrhage. Neither destruction of the bony orbit nor venous anomaly was evident on the CT.

Other investigations, including full blood examination and clotting function tests, gave normal results.

Follow-up of the patient showed complete regression of the proptosis, ptosis, and ecchymosis, as well as a return of ocular movements to normal within three weeks. A CT scan performed one month later was normal (Fig 2).

## Discussion

Acute OH is a rare occurrence which has been associated with strain. Law[2] reported it caused by moderate physical exertion in two healthy males. Vision was not affected, but there was a slight proptosis, diplopia, and limitation of ocular movements. The condition subsided completely without intervention within two to three weeks. Recently Katz and Carmody[3] reported a case of mild subperiosteal haematoma induced by the Valsalva manoeuvre. Here again the haemorrhage resolved spontaneously within three weeks. In this case, as in the previous two cases, the patient was a young, 23-year-old sportsman (weight lifter).

Labour has been reported only once as being associated with OH.[3] In our case it was certainly the cause of the OH, since it appeared three times during labour in the same woman and no other underlying condition was detected, though the possibility of a small haemangioma or lymphangioma not visualised by computed tomography remains. The cause of OH following a strain is probably increased intra-abdominal and intrathoracic pressure. Since the orbital vein contains no valves, the pressure is transmitted freely to the orbital blood vessels causing orbital congestion and finally rupture of the vessel walls and haemorrhage. As long as there is no visual loss requiring surgical drainage these patients can be safely observed for expected resorption of the haemorrhage within a few weeks.

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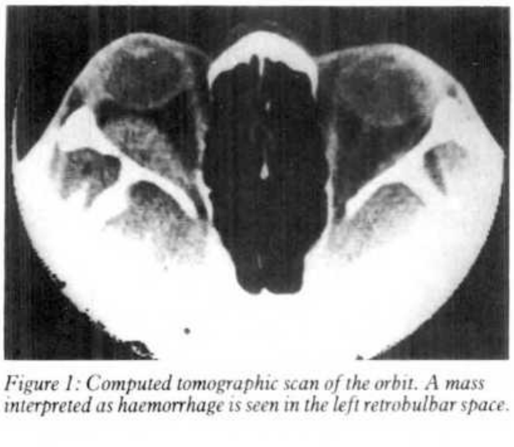

*Figure 1: Computed tomographic scan of the orbit. A mass interpreted as haemorrhage is seen in the left retrobulbar space.*

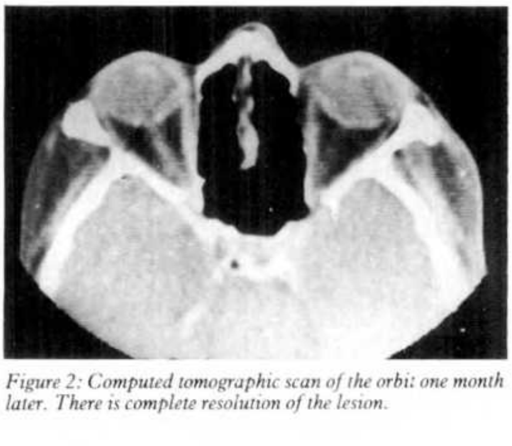

*Figure 2: Computed tomographic scan of the orbit one month later. There is complete resolution of the lesion.*

*British Journal of Ophthalmology*, 1990, **74**, 243–244

# Loss of vision in one eye following scoliosis surgery

J West, G Askin, M Clarke, S A Vernon

**Abstract**

**A 50-year-old woman developed left sided total external ophthalmoplegia and complete visual loss, with evidence of choroidal non-perfusion, immediately following scoliosis surgery. The ocular movements recovered, but the eye remained blind. It is suggested that these lesions may have resulted from pressure on the orbital contents during surgery.**

The case is reported of a 50-year-old woman who developed unilateral total external ophthalmoplegia and blindness following scoliosis surgery.

### Case history

A 50-year-old nurse was seen at the back pain clinic in June 1986. She had undergone a spinal fusion for scoliosis at the age of 15 but had suffered persistent pain and intermittent claudication since. In April 1987 she was operated on for decompression at levels L1, L2, and L3 followed by stabilisation with Harrington distraction rods, supplemented by wires passed under the lamina and secured to the rods.

Anaesthetic induction was with propofol, fentanyl, and droperidol. Atracurium (total dose 55 mg), fentanyl (total dose 350 mg), chlorpromazine (total dose 7·5 mg) and labetalol (total dose 10 mg) were given at intervals throughout the operation. During the operation she was positioned prone with the eyes covered by a gauze swab and tape. The anaesthetic time was 4½ hours. Care was taken to avoid pressure on the eyes. Total blood loss was estimated at 1 litre, and the systolic blood pressure was maintained at between 70 and 90 mmHg throughout the procedure.

Immediately after the operation the patient noted complete, painless visual loss in the left eye. The left orbit was observed to be congested and the left eye proptosed. External ocular movements were absent. The left corneal reflex was reduced. The left pupil was fixed and mid-dilated. The left optic disc was pale and the retinal vessels attenuated. The right eye was normal.

Cavernous sinus thrombosis was suspected, but not confirmed either by C T or magnetic resonance imaging (Fig 1). Treatment was instituted with intravenous antibiotics and anticoagulants. Three months later the left eye had no perception of light and was divergent and hypertropic. External ocular movements had recovered, but adduction was painful and limited. The left corneal reflex was reduced. There was no iris atrophy. Examination of the fundus showed evidence of choroidal and retinal non-perfusion (Fig 2).

### Discussion

Sudden loss of vision following general and orthopaedic surgery has been reported,[1 2] but to our knowledge no previous case has been associated with ophthalmoplegia or such striking involvement of the choroidal circulation. In previous cases the mechanism of visual loss was infarction of the retina or optic nerve following hypotension or embolism. The ophthalmoplegia seen in our patient could have been due to cavernous sinus thrombosis. However, this rarely causes permanant loss of vision,[3] and there was no evidence of thrombosis on MRI scan.

Hollenhorst *et al* reported eight cases of unilateral blindness following neurosurgical procedures in 1954.[4] These patients either lay prone or were sitting with the face cushioned on a headrest. The clinical features in these patients were similar to our own case. They reproduced the lesion experimentally in monkeys using a combination of hypotension and pressure on the orbit.

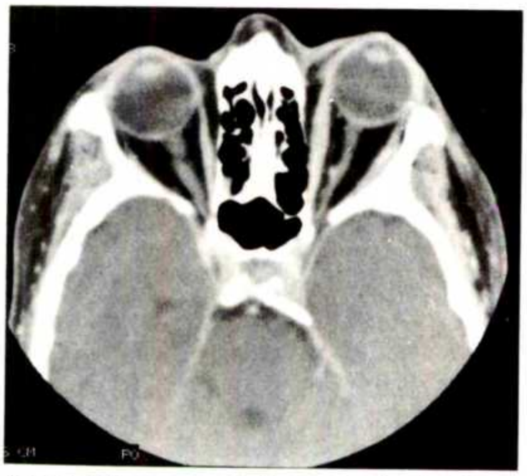

*Figure 1: C T scan one week after operation showing left proptosis and swelling of left medial rectus but no abnormality in the cavernous sinus.*

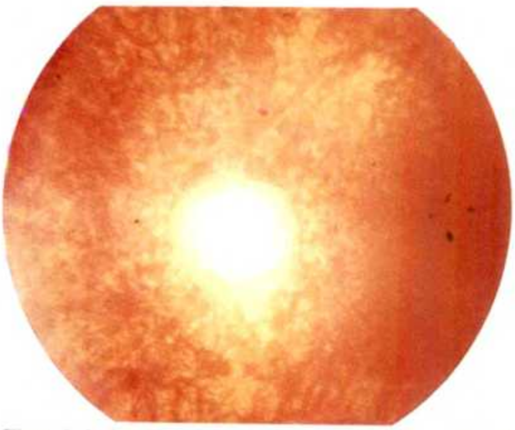

*Figure 2: Left optic disc showing pallor and loss of retinal and choroidal vessels.*

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Acute ischaemic lesions involving the choroid are rare. This rarity is thought to be because of communications between the adjacent choroidal segments via the vortex veins.[5] Amalric reported the case of a 34-year-old woman who lost the vision of one eye following mammoplasty.[6] The fundal appearances were similar to those in our case. There had been no perioperative hypotension, and perioperative ocular compression was thought to be the cause. We believe this to be the likely cause of injury in our patient. Prolonged compression of the orbital contents during anaesthesia can give rise to ocular and orbital ischaemia, causing blindness and ophthalmoplegia, and adequate protection should be given to the eyes during procedures where such compression might occur.

We thank Dr A M Whiteley and Mr J Webb for helpful discussion and permission to report this case and Dr T Jaspan for interpreting the radiographs.

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# Ocular cowpox: transmission from the domestic cat to man

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**Abstract**

**A clinicopathological case of ocular cowpox is reported. Cowpox is no longer regarded as being enzootic in cattle. The most likely mode of transmission of cowpox to man appears to be from the domestic cat or wild rodents.**

A previously healthy 18-year-old male student was admitted to hospital in July 1988. He gave a two-day history of left facial swelling and discomfort, followed 24 hours later by what he described as a 'stye' on his left upper lid. His general practitioner started him on flucloxacillin 250 mg four times a day and considered the most likely diagnosis to be mumps. Subsequently, he developed gross left facial swelling and periorbital oedema.

The previous month was spent working in his garden, which is adjacent to a farm in which cows reside. The patient owned a 7-year-old male cat, which scratched him on the upper left chest three weeks before an influenza-like illness and his initial presentation. The cat had had a previously recorded rash, treated with hormone replacement tablets by the local veterinary surgeon.

Examination revealed visual acuities of 6/6 right and left eye. Both eyes were white and uninflamed and moved normally. There was no evidence of keratoconjunctivitis. The positive clinical findings were a grossly swollen left upper lid and side of face, with associated lymphadenopathy involving the parotid, preauricular, and submandibular glands. There was concomitant ulceration of both left lids medially, with scattered infected nodules mainly in his upper lid. Systemic examination gave otherwise normal results.

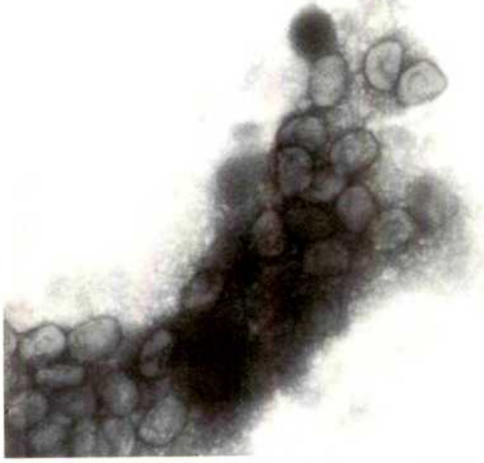

*Figure 2: Electron micrograph showing large numbers of cowpox virus. (×20 000.)*

Specific investigations included full blood count, blood culture, and an eye swab for culture and microscopy. Subsequently group I poxvirus was isolated, and further investigations, including electron microscopy, confirmed this to be cowpox. The patient had a neutralising titre of 512 and the cat's titre was 64. Both are compatible with infection, but in the case of the cat the exact timing of infection cannot be determined. It is most likely that the patient's eye was self inoculated from the lesion on his chest. His condition has now fully resolved and he is pursuing his chosen university career.

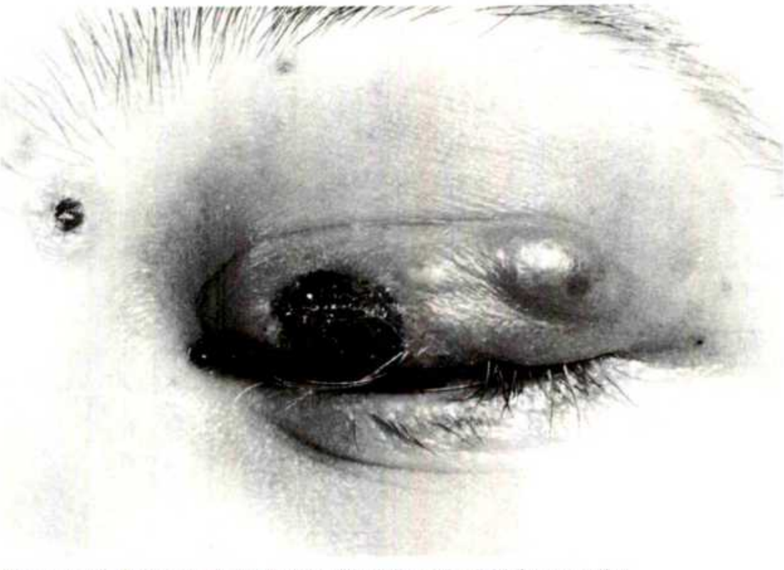

*Figure 1: Erythematous ulcerated upper lid 10 days after initial presentation.*

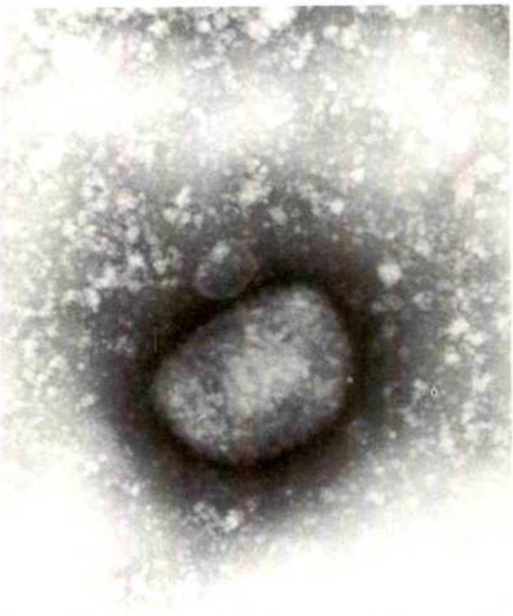

*Figure 3: Electron micrograph showing morphology of a single cowpox virus. (×48 000.)*

## Discussion

Cowpox has always had a special place in the history of medicine since Edward Jenner first demonstrated in 1798 that immunity to smallpox could be induced by inoculation of material from an animal disease which he called 'cowpox'.[1] Our understanding of the transmission of cowpox has changed in recent years, specifically as regards its being enzootic in cattle.[2] Transmission from the domestic cat or some wild rodent now appears to be the most likely mode of transmission of cowpox to man.[3]

Cowpox was previously thought to be enzootic in cattle and to be an occupational hazard for farm workers.[2] Bovine cowpox is rare in cattle, and most human cases occur without any contact with farm animals.[4] The suggestion that cowpox virus circulates in a separate domestic or wildlife reservoir therefore gained acceptance in the early 1980s.[5]

Cowpox infection was first recognised in the domestic cat in 1978,[6] though cases were seen in captive cheetahs the previous year.[7] Twenty to 30 new feline cases are now seen annually by the Bristol and Liverpool University laboratories.[8] Cats are probably not the original reservoir, as infected cats often show evidence of bites, consistent with a wildlife reservoir.[9] The reservoir has not been found, but orthopoxvirus antibodies due to cowpox infection are present in some woodmice and voles[10] and a closely related virus circulates in Russian rodents.[11]

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*British Journal of Ophthalmology*, 1990, **74**, 247–248

# Mixed haematogenous endophthalmitis caused by *Candida albicans* and CDC fermentative corynebacterium group A-4

Caroline Barker, Jane Leitch, N P Brenwald, M Farrington

## Abstract

**We report a case of mixed haematogenous endophthalmitis in which *Candida albicans* and Centres for Disease Control (CDC) corynebacterium group A-4 were isolated together from an aspirate of vitreous humour.**

## Case report

A 77-year-old retired farmer was admitted to hospital in May 1987 as an emergency with a six-hour history of nausea and abdominal pain. His past medical history included a shotgun injury to his left eye resulting in enucleation at age 5, penicillin allergy, and a prostatectomy. A chest *x*-ray showed gas under the right hemidiaphragm. A perforated duodenal ulcer was oversewn at laparotomy. A Polya gastrectomy was performed six days later for persistent melaena. Postoperatively the patient became dehydrated, with a persistently high blood glucose, which responded to an insulin sliding scale and transfusion via a right jugular central venous line. The patient was transferred to the Intensive Therapy Unit, where he received total parenteral nutrition via the central line, which was in situ for 10 days. After removal the tip of the line grew *C albicans*. At this time his peripheral white blood cell count was $29{\cdot}5 \times 10^9$/l. Abdominal drain fluid grew *C albicans* and a diphtheroid, which was not further identified, and repeated blood cultures were sterile. During the first three postoperative weeks he was intermittently febrile, and he received various combinations of gentamicin, metronidazole, cefotaxime, erythromycin, co-trimoxazole, and trimethoprim.

On the 19th postoperative day the patient complained of blurred vision in the right eye. On referral to the Ophthalmology Department his vision was 6/60+1, and he was noted to have a marked anterior uveitis and an isolated area of focal chorioretinitis associated with vitreous activity. He was treated initially with topical steroids, which produced a subjective improvement. However, this was not maintained, and the posterior uveitis progressed. A lesion along the supratemporal vessels developed that was associated with beaded intravitreal abscesses. Serological tests for toxoplasma, syphilis (VDRL, TPHA), cytomegalovirus, and herpes simplex virus were negative. A presumptive diagnosis of candida endophthalmitis was made, and a vitrectomy was performed.

A Gram-stained smear of the vitreous washings showed occasional yeasts and large numbers of intracellular pleomorphic Gram-positive bacilli. In view of his deteriorating renal function the patient was treated with oral 5-flucytosine 2 g twice daily (with regular serum assay) and ketoconazole 400 mg once daily, with topical cefotaxime and gentamicin. A serological test for *C albicans* performed at the Mycology Reference Laboratory, Colindale, London, was positive (precipitin titre 1:4, agglutination titre <1:4), and the washings grew scanty yeast colonies and a heavy growth of a Gram-positive bacillus after 48 hours' incubation.

Ten days later an exudative retinal detachment began temporally and extended to become total. A vitreous washout was performed, but specimens were not sent for culture. The retinal detachment persisted, and the vision was perception of light. Over the following month a dense cataract developed, but the retinal detachment flattened spontaneously. Topical antibiotics were stopped after three weeks, and the patient was discharged nine weeks after admission on oral antifungal therapy which was stopped after a total course of four weeks. Lensectomy, vitrectomy, and division of membranes were performed when his general health had improved, resulting in improvement of vision to 6/36+1. In December 1987 an inferior tractional retinal detachment was noted and repaired with injection of silicone oil.

Over the next six months vision improved to 6/18. The patient has had two episodes of urinary frequency with associated pyuria occurring four months and seven months after his initial admission. Urine specimens on both occasions grew *C albicans* ($>10^5$ colony forming units /ml) and symptoms resolved after short courses of oral 5-flucytosine. He has had no further ocular or urinary symptoms and is managing well with low visual aids.

### MICROBIOLOGY

The yeast was identified as *Candida albicans* by the Mycology Reference Laboratory, Central Public Health Laboratory, Colindale, London, and found to be sensitive to 5-flucytosine, amphotericin B, ketoconazole, and miconazole. The bacterium was a strictly aerobic coccobacillus that formed yellow pigmented colonies after 48 hours' incubation on equine blood agar at 37°C. It was non-motile at 37°C and room temperature, catalase and Voges-Proskauer positive, and DNAase, urease, and nitrate reductase negative. It produced acid from glucose, fructose, mannose, maltose, and mannitol but not from lactose, trehalose, xylose, sucrose, melibiose, or raffinose, and it was sensitive to penicillin and vancomycin by disc

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diffusion. It was identified by Dr Weaver, Centres for Disease Control, Atlanta, Georgia, USA as belonging to CDC fermentative corynebacterium group A-4.

## Discussion

To our knowledge this is the first reported case of metastatic endophthalmitis caused by CDC fermentative corynebacterium group A-4, and the first case of mixed haematogenous endophthalmitis involving *C albicans*. The majority of cases of infectious endophthalmitis follow direct inoculation by trauma or surgery. A great variety of organisms have been isolated (including *C albicans*[1] and CDC fermentative coryneform group A-4[2]), and mixed cultures are not uncommon. Haematogenous endophthalmitis, however, is much less frequent. Because of their underlying associated medical conditions these patients may present to any hospital specialty, and this may lead to delayed diagnosis and treatment. The commonest isolate is *C albicans*, which often follows prolonged antibiotic therapy, intravenous therapy,[3] or intravenous drug abuse.[4] Other organisms believed to have spread to the vitreous via the blood include staphylococci, streptococci, *Neisseria meningitidis*, Gram-negative rods,[5] mycobacteria,[6] and *Aspergillus fumigatus*.[7] A single case of mixed haematogenous endophthalmitis has been reported in which a Lancefield group G β-haemolytic streptococcus and two strains of coagulase-negative staphylococci were isolated from the vitreous of a patient with streptococcal cellulitis of the leg.[8]

Non-diphtheria corynebacteria are components of the normal flora that pose the clinical diagnostic laboratory considerable problems of identification, and few defined clinical syndromes have yet been associated with individual species. Therefore many isolates are dismissed as contaminants. Fermentative corynebacterium CDC group A-4 has been associated with infections at many body sites including blood, cerebrospinal fluid, urine, sputum, and pleural fluid,[9,10] but it shares with the closely related fermentative corynebacterium CDC group 1 an apparent predilection for causing endophthalmitis. Further studies on the taxonomy and clinical significance of fermentative corynebacteria are needed to define their pathogenic abilities more accurately. In our case the significance of the bacterial isolate is confirmed by its intracellular location in vitreal polymorphs and isolation in heavy growth, but its contribution to the local septic process is impossible to assess. Whereas vitrectomy is the recognised treatment for candida endophthalmitis, the additional value of systemic or local antifungal agents is disputed, but the balance of opinion favours the use of systemic 5-flucytosine and ketoconazole.[3] Although suffering a mixed fungal and coryneform infection, our patient responded well to vitrectomy, oral antifungal agents, and topical antibiotics.

Candida endophthalmitis is a largely avoidable iatrogenic complication. Candidaemia is rarely suspected or detected at the time it occurs, but repeated questioning about visual disturbance in patients treated with antibiotics and indwelling intravenous catheters who become febrile may alert the clinician to the presence of endophthalmitis at an early stage in its development.

We thank Mr D W Flanagan for permission to report this case, and Professor D W R MacKenzie (Mycology Reference Laboratory, Central Public Health Laboratory, Colindale, London) and Dr R E Weaver (Director, Special Bacteriology Section, Centres for Disease Control, Atlanta, Georgia, USA) for confirming the identity of the organisms.

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# Ocular brucellosis

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## Abstract

**Though brucellosis has been eradicated from many countries, it remains a health problem in many developing countries. We report hereon a 34-year-old woman who presented with recurrent attacks of uveitis unresponsive to treatment with steroids. She was found to have systemic brucellosis, and *Brucella melitensis* was isolated from a paravertebral abscess. The condition responded to systemic antibiotics, and she completely recovered from her uveitis.**

Brucellosis is a zoonotic disease caused by the Gram-negative bacteria *Brucella melitensis* or *B abortus*. It is transmitted from animals to man through the ingestion of unpasteurised milk, milk products, or uncooked meat.[1] Transmission has also been reported by airborne spread[2] and by beauty skin creams prepared from bovine placental extracts.[3] The disease has a worldwide distribution and the incidence may vary from one country to another. Although it has been erradicated or got under control in most western countries, it remains a health problem in many developing countries.

The main purpose of this communication is to report a case of chronic brucellosis with uveitis and isolation of the organism.

## Case report

A 34-year-old Saudi female presented with a history of recurrent episodes of redness and pain in the left eye associated with temporal headaches and tearing of nine years' duration. She was seen by several ophthalmologists and was given repeated courses of topical and systemic corticosteroids until she became cushingoid and developed diabetes mellitus, which she has had for the past four years. She had no symptoms in the right eye, but she complained of bilateral flank pains, with recurrent episodes of fever. Four years earlier the patient had recurrent arthritis of the knee joints and interphalangeal joints. She gave a history of ingestion of unpasteurised milk on several occasions in the past.

A general physical examination showed an obese febrile patient with a temperature of 39·7°C. Her visual acuity was 20/40 corrected to 20/20 in the right eye and 20/100 in the left eye. Her vision improved with a pinhole to 20/60 in the left eye.

Biomicroscopic examination gave normal findings in the right eye. Biomicroscopy of the left eye showed deep violaceous perilimbal discoloration of the sclera, and the sclera was swollen; it was also tender to pressure. The cornea was clear, with large, whitish-yellow keratic precipitates. There was no limbal or corneal infiltration or opacities. The anterior chamber showed 1+ flare and 1+ cells. The pupil was regular and reactive to direct and consensual light, and the lens showed very early posterior subcapsular opacities. Biomicroscopy of the anterior vitreous showed cells but no exudates. Ophthalmoscopic examination of the right eye revealed a normal optic nerve head, blood vessels, and macula. The left eye showed clinical evidence of choroiditis which appeared to be geographic measuring 7×4 mm in the superior nasal quadrant.

Repeated blood cultures were negative. The blood titre for *Brucella (abortus* and *melitensis)* was 1:1644. A chest x-ray showed a soft tissue shadow in the area of T8 to T10. Tomography showed a large lytic area in the central and left half of the vertebral body T9. There was some irregularity of the lower articular surface of T9. A large left paravertebral mass was present. A total body gallium scan showed increased activity in the lower thoracic vertebrae.

Aspiration of a paravertebral abscess revealed pus cells with many neutrophils and Gram-negative organisms; on culture these were shown to be *Brucella melitensis*.

The patient was started on streptomycin, intra-muscular injection of 1 g daily for eight consecutive days, together with doxycycline 100 mg orally and rifamycin 300 mg twice daily. The streptomycin was discontinued after three weeks of treatment, and the doxycycline and rifamycin were continued for three months. A repeat gallium scan after two weeks' treatment showed a decrease in the size of the abscess, and a blood count showed leucocytes $5{\cdot}7\times10^9$/l, haemoglobin 10 mg/dl, and sedimentation rate of 16 mm in the first hour.

The patient's symptoms improved dramatically, and ocular examination showed a decrease in the cells and flare in the left eye, with improvement of vision to 20/60 and decrease in the choroidal infiltration to an area of 1·5×3 mm. The impairment of visual acuity in the left eye was thought to be due to the posterior lenticular subcapsular opacities.

## Discussion

This case report emphasises the fact that brucellosis remains an important health problem in many developing areas and that some patients with brucellosis may present with uveitis. The disease is curable if discovered early and treated promptly. The diagnosis of brucellosis was missed in this patient for nine years, and she was treated with systemic steroids. Since uveitis secondary to brucellosis is curable, it is recommended that patients with chronic granulomatous uveitis be examined for brucellosis. Systemic brucellosis is not uncommon, and patients may present with a clinical picture similar to that of tuberculosis. In fact the patient was first suspected of having tuberculosis. Following treatment this patient remained symptom free for two years and did not require topical or systemic steroids to control her uveitis. Tourists and visitors to developing countries may acquire the infection during their visits and may occasionally develop the illness on their return to their country of origin.[4]

In view of the fact that brucellosis may present with vague and non-specific symptoms, a positive history of ingestion of unpasteurised milk or milk products should arouse suspicion. In some developing countries the milk is not pasteurised before the preparation of cheese, so that this too may transmit the disease from animals to man.

The clinical findings in this patient consisted of anterior granulomatous uveitis, vitreous inflammatory cells, and posterior choroiditis. In addition she had evidence of scleritis, which responded to the antibiotic therapy. The anterior granulomatous uveitis was chronic and did not respond to topical steroids. The patient persisted in having smouldering, recurrent episodes of uveitis until definitive systemic antimicrobial agents for brucellosis were given.

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# External ocular pigmentation secondary to perforating eye injury

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**Abstract**

**The dispersal of pigment centrifugally through the conjunctiva from the site of a repaired traumatic perforation was observed. Iris tissue had been incarcerated in the wound for three days prior to surgical repair. Conjunctival biopsies were examined by light and electron microscopy. Light microscopy revealed a normal, non-pigmented conjunctival epithelium and numerous pigment-laden cells in the substantia propria. Electron microscopy showed these cells to contain melanosomes closely resembling those found in normal iris posterior pigment epithelium. The causes of abnormal external ocular pigmentation are discussed.**

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Pigmentation of the conjunctiva may be melanocytic or non-melanocytic in origin. Melanocytic lesions of the conjunctiva include benign racial pigmentation, ocular melanocytosis, oculodermal melanocytosis, naevi, melanoma, and acquired melanosis.[1,2] In the last case this may be primary acquired melanosis or secondary to a variety of conditions, including radiation, Addison's disease, pregnancy, chemical toxicity, and chronic conjunctivitis. We report here a case of acquired pigmentation of the conjunctiva and episclera related to the migration of iris pigment epithelial cells from a traumatic perforation of the globe.

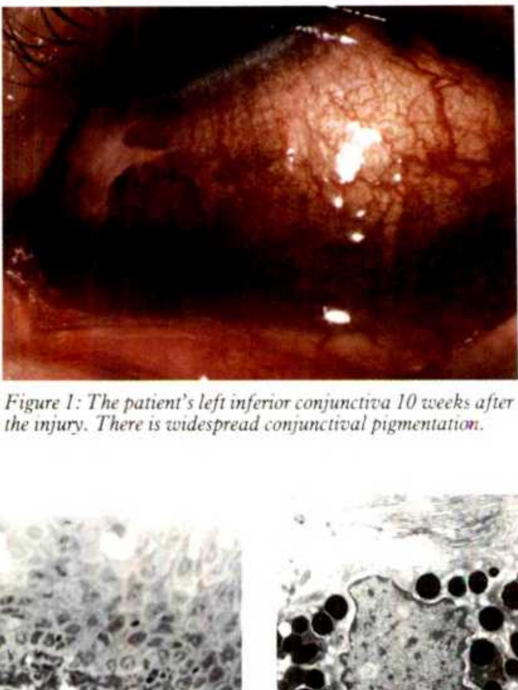

*Figure 1: The patient's left inferior conjunctiva 10 weeks after the injury. There is widespread conjunctival pigmentation.*

## Case report

A 51-year-old white male attended the Ophthalmic Emergency Department complaining of a foreign body sensation and blurred vision in his left eye. While chopping wood three days earlier he had been struck in the left eye with a piece of wood but had not sought medical attention immediately.

On examination his visual acuity was 6/6 right and 6/36 left. The left conjunctiva was injected and chemosed, particularly in the inferonasal quadrant. The pupil was peaked inferonasally. The anterior chamber was formed and contained moderate numbers of inflammatory cells. The right eye was normal and showed no pigmentary anomaly.

The left eye was examined under anaesthesia, and a circumferential inferonasal limbal perforation was found. Incarcerated uveal tissue was noted within the wound. The conjunctiva in the immediate vicinity of the wound was deeply pigmented. The incarcerated uveal tissue was

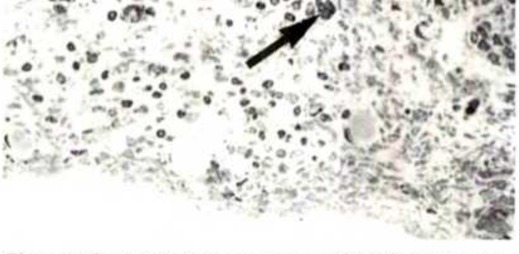

*Figure 2: Conjunctival biopsy examined by light microscopy. There are numerous pigment-laden cells (arrowed) in the substantia propria. (×210).*

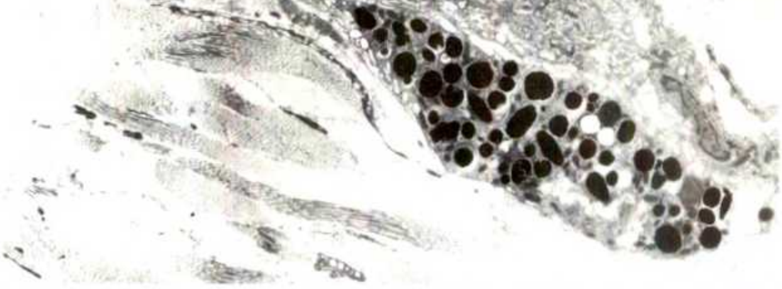

*Figure 3: Electron micrograph showing pigment-laden cells in the substantia propria. (×3900).*

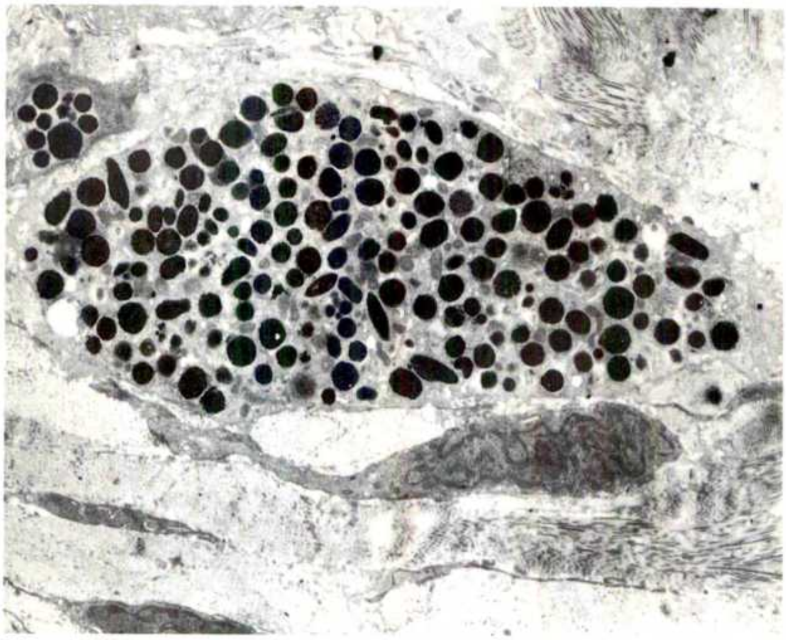

*Figure 4: Electron micrograph showing cell containing melanosomes at various stages of development. (×5000).*

excised, and the wound was repaired with three 8/0 virgin silk sutures. The conjunctiva was repaired with 8/0 Vicryl, and subconjunctival injections of gentamicin and mydricaine were given.

Postoperatively the patient made a satisfactory recovery and was discharged five days later on a combination of topical antibiotics, steroids, and a mydriatic. He was re-examined 10 days postoperatively, when it was noted that the conjunctival pigmentation was no longer confined to the immediate vicinity of the wound but was distributed throughout the inferior conjunctiva and fornix. Ten weeks after the injury the conjunctival pigmentation was still apparent (Fig 1). Several small biopsy specimens were taken from the inferotemporal conjunctiva, and these were studied by light and transmission electron microscopy.

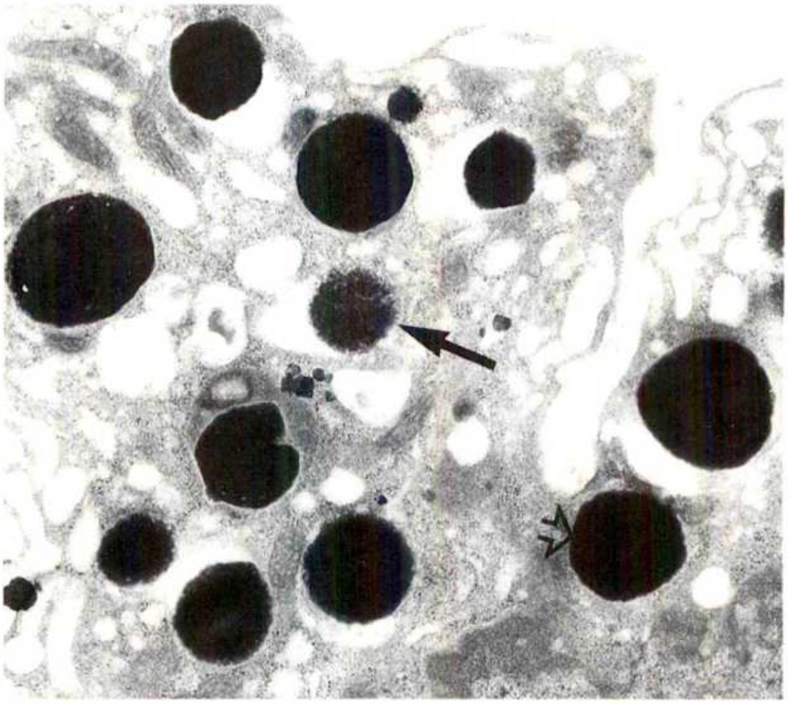

*Figure 5: Electron micrograph showing stage III (partially melanised, dark arrow) and stage IV (fully melanised, light arrow) melanosomes. (×20 000).*

### METHODS

Biopsy material for light microscopy was fixed in 10% buffered formaldehyde and processed into paraffin wax. Sections were stained with routine stains, with and without bleaching with potassium permanganate, and the Fontana method was used to test for melanin.

For electron microscopy, tissue was fixed in 3% phosphate buffered glutaraldehyde for one hour at 4°C. The tissue was then washed in 0·2% sucrose, postfixed in 1% osmium tetroxide for two hours at 4°C, and dehydrated in ascending grades of alcohols and epoxypropane. The tissue was embedded in Araldite, and ultrathin (60 nm) sections were cut. These were stained with uranyl acetate and lead citrate and examined under a Philips 400 electron microscope.

## Results

*Light microscopy* showed a normal non-pigmented conjunctival epithelium. Numerous pigment-laden cells were observed in the substantia propria (Fig 2). A scanty inflammatory infiltrate was also noted within the substantia propria.

*Electron microscopy* confirmed the presence of pigment-laden cells within the substantia propria (Fig 3). These cells contained numerous stage IV (mature) melanosomes and occasional stage III melanosomes (Figs 4 and 5). The melanosomes were round, oval, and occasionally extremely elongated, closely resembling those found in the normal iris posterior pigment epithelium (Fig 6). Occasional inflammatory cells were noted within the substantia propria.

## Discussion

Abnormal external ocular pigmentation may be divided into two broad categories: congenital or early acquired type, and late acquired type.[1] Melanosis oculi, oculodermal melanosis, and conjunctival naevi are examples of congenital or early acquired abnormal external ocular pigmentation. These lesions may be noted in early childhood and often show increased pigmentation at puberty or in early adult life. External ocular pigmentation acquired in later life may be benign, premalignant, or malignant.[3-7] Benign acquired external ocular pigmentation may be secondary to a variety of factors, including radiation, metabolic disorders, chemical toxicity, and chronic inflammatory diseases of the conjunctiva.

The patient described in this report appears to have benign acquired external ocular pigmentation secondary to the dispersal of iris pigment epithelial cells following incarceration of the iris at the site of a perforating eye injury. Some normal pigmentation may have been present prior to the injury, but the patient firmly denied any prior ocular pigmentation, and the pigmentation appeared to disperse with time centrifugally from the perforation site,

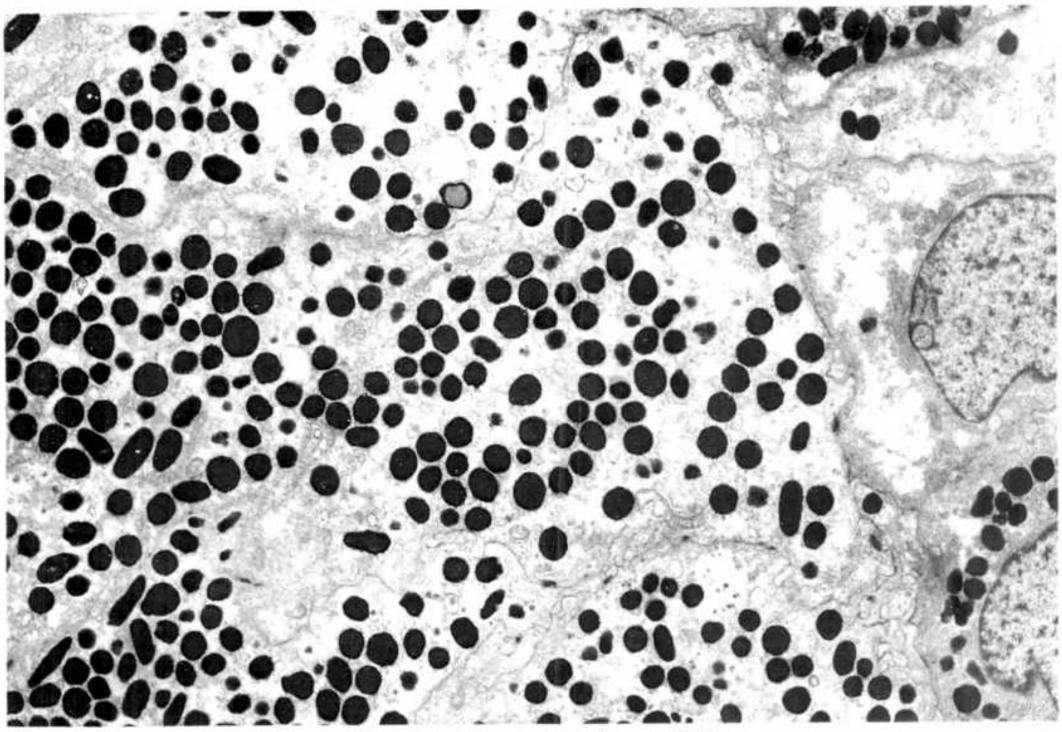

*Figure 6: Electron micrograph of normal iris posterior pigmented epithelium.* (×*3900*).

suggesting that it was related to the injury. The shape and size of the melanosomes within the pigmented cells further support this argument. The melanosomes found in the retinal pigment epithelium and posterior pigment epithelium of the iris are in general larger than those found in skin or conjunctival epithelium.[8] Indeed the morphology of these pigmented cells would seem to be similar to those of the posterior pigment epithelium of the iris (Figs 3–6).

We conclude that dispersion of pigment cells through a perforation represent another, albeit rare, cause of acquired external ocular pigmentation.

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# LETTERS TO THE EDITOR

## A patient's ingenuity in the management of lagophthalmos

SIR,—Suffering from lagophthalmos after repair of bilateral blepharoptosis, a 65-year-old man fitted rolls of cloth to an old spectacle frame to elevate his lower lids, thus relieving his symptoms at night.

A 65-year-old male underwent repair of bilateral blepharoptosis with a fascia lata sling. After surgery he suffered from lagophthalmos and exposure keratitis of the lower third of both corneas despite conservative treatment with artificial tears and ocular lubricants. While awaiting surgery to repair the overcorrected ptosis, he looked for a way to alleviate irritation and pain which bothered him espcially at night. When he had not found an efficient way to bring both upper lids down, and thus close the eyes, he tried to achieve complete eyelids closure by elevation of the lower lids.

He built a device composed of two strips of flannel cloth rolled and mounted on hinges, and attached to an old spectacle frame (Fig 1). By wearing the glasses and pulling the ends of the rolled strips downwards (like shades), both lower lids became elevated, and thus enabled the eyelids to close (Fig 2). Wearing these spectacles at night during sleep, our patient was relieved from his symptoms.

We submit this report not only to show the patient's ingenuity but also to suggest that similar devices might be used in some cases of lagophthalmos as a temporary means of treatment.

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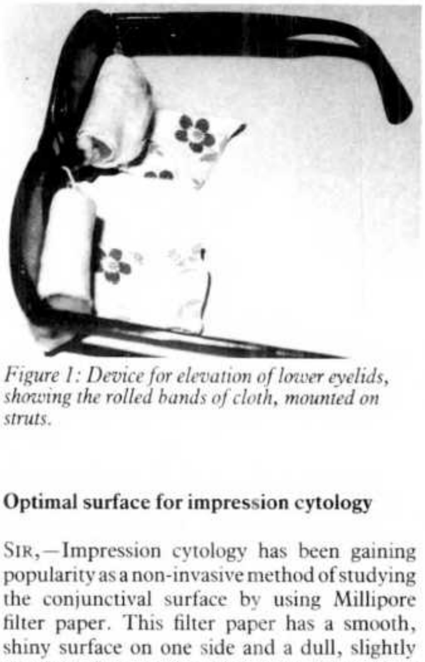

*Figure 1: Device for elevation of lower eyelids, showing the rolled bands of cloth, mounted on struts.*

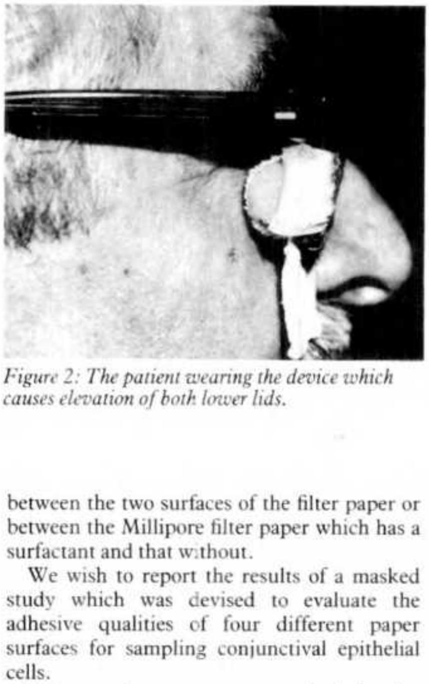

*Figure 2: The patient wearing the device which causes elevation of both lower lids.*

## Optimal surface for impression cytology

SIR,—Impression cytology has been gaining popularity as a non-invasive method of studying the conjunctival surface by using Millipore filter paper. This filter paper has a smooth, shiny surface on one side and a dull, slightly rough surface on the other side. It has been claimed that the dull surface provide a better yield of conjunctival cells while the smooth surface is more suitable for studyiung mucus.[1,2] Moreover, the Millipore filter paper with surfactant, which is normally present in the filter paper, has been claimed to be less suitable for obtaining conjunctival cells than one without surfactant.[1] On the other hand Tseng[3] did not find any difference in cell adhesiveness between the two surfaces of the filter paper or between the Millipore filter paper which has a surfactant and that without.

We wish to report the results of a masked study which was devised to evaluate the adhesive qualities of four different paper surfaces for sampling conjunctival epithelial cells.

Fifteen volunteers were recruited for the study. For each subject one of each of four Millipore filter paper surface types was applied to one of each of four sampling sites. The four sampling sites were the temporal and nasal bulbar conjunctiva of both eyes of each subject. The filter paper surfaces used were dull dry and smooth dry, both with surfactant, and dull wet and smooth wet, both without surfactant. The type of collecting surface was assigned strictly at random by tables of random numbers and standard methods, to the sampling location.

TABLE I *Yield of cells*

| *Subject* | *Shiny and wet* | *Shiny and dry* | *Dull and dry* | *Dull and wet* |
|---|---|---|---|---|
| 1 | 1 | 0 | 0 | 3 |
| 2 | 0 | 0 | 3 | 3 |
| 3 | 0 | 3 | 3 | 3 |
| 4 | 1 | 2 | 2 | 3 |
| 5 | 0 | 2 | 2 | 3 |
| 6 | 0 | 0 | 1 | 0 |
| 7 | 2 | 0 | 3 | 3 |
| 8 | 0 | 0 | 0 | 1 |
| 9 | 0 | 1 | 3 | 3 |
| 10 | 0 | 0 | 2 | 3 |
| 11 | 0 | 0 | 2 | 3 |
| 12 | 0 | 0 | 3 | 3 |
| 13 | 0 | 0 | 3 | 1 |
| 14 | 0 | 0 | 1 | 2 |
| 15 | 1 | 1 | 2 | 3 |

0=nil to very few cells. 1=few cells. 2=many cells. 3=abundant cells.

The results are shown in Table I. Friedman's method for non-parametric analysis of variance for randomised blocks[4] together with the related critical range method of Wilcoxon[4] were applied to the data. Dull surfaces were found to give a significantly better yield of epithelial cells than did the smooth type ($0·01<0\ p<0·05$ for dry filter paper; $p<0·01$ for wet filter paper). Adams[1] and Nelson *et al*[2] also found the dull surface to be superior. On the other hand the performance of our filter paper types did not alter significantly with the presence or absence of surfactant ($p > 0·05$ for both dull and smooth surfaces). Adams'[1] finding that the presence or absence of surfactant affected the collection process is therefore not replicated in our study.

R F REFAAT
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## Ocular melanoma

SIR,—With regard to the correspondence on ocular melanoma by A B Tullo *et al*[1] and J Hungerford[2] we would like to report some of our experience with radioimmunoscintigraphy (RIS) with antibody 225·28S in ocular melanoma.

We initially performed RIS in 16 patients with a certain clinical diagnosis of malignant melanoma. Images were made at six hours after injection of the antibody. Planar scintigraphy yielded detection of the melanoma in only six cases (37·5%). The use of a double pinhole collimator showed significantly higher activity in the melanomatous eye in 13 of 16 cases (81%).[3] RIS was also performed in a second group of five patients with variable diagnoses. The diagnosis was based on the clinical course and the results of other diagnostic tests. In one case we are not sure of the diagnosis naevus; however, the patient has been without clinical signs of growth of the lesion for four years now. RIS with a regular gamma camera was negative in all cases (Table I). Pinhole scintigraphy yielded several false positive results and therefore is not reliable.

To increase the sensitivity of RIS we decided to perform planar scintigraphy at four and six hours after injection as well as single photon emission computerised tomography (SPECT) at six hours after injection.[4] The second image enables us to measure the tracer uptake over a course of time. Tracer uptake in the tumour can be seen at four hours after injection and becomes more clearly delineated six hours after injection. In a recent series of six melanoma patients five tumours could be visualised with planar RIS or SPECT (83%).

From these results we consider that RIS in melanoma patients can be a helpful additional diagnostic investigation provided the technical conditions are carefully considered. The

TABLE I *Patients with various diagnoses*

| *Patient* | *Sex* | *Age* | *Diagnosis* | *FA* | *USG* | *RIS* |
|---|---|---|---|---|---|---|
| 1 | F | 88 | Disciform macular degeneration with subretinal haemorrhage | NA | – | – |
| 2 | M | 24 | Haemangioma | ± | – | – |
| 3 | M | 66 | Naevus or melanoma | ± | ± | – |
| 4 | F | 70 | Rectinal pigment epithelial hyperplasia | ☆ | – | – |
| 5 | M | 47 | Retinal pigment epithelial dystropy | – | – | – |

FA = fluorescein antiography. USG = ultrasonography. RIS = radioimmunoscintigraphy. NA = not available. ☆ = not available due to peripheral localisation.

possibility of a false positive result due to tracer uptake in a naevus should be kept in mind.

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1 Tullo AB, Dodd CL, Noble JL, Owens S, Rao H. Ocular melanoma. *Br J Ophthalmol* 1989; **73**: 771.
2 Hungerford J. Ocular melanoma. *Br J Ophthalmol* 1989; **73**: 772.
3 Schaling DF, Van Kroonenburgh MJPG, Borsje RA, *et al.* Radioimmunoscintigraphy with melanoma associated monoclonal antibody fragments in ocular melanoma. *Graefes Arch Clin Exp Ophthalmol* 1989; **227**: 291–4.
4 Bomanji J, Nimmon CC, Hungerford JL, Solanski K, Granowska M, Britton KE. Ocular radioimmunoscintigraphy: sensitivity and practical considerations. *J Nucl Med* 1988; **29**: 1038–44.

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# BOOK REVIEWS

**Proliferative Vitreoretinopathy (PVR).** Eds H MacKenzie Freeman, Felipe I Tolentino. Pp 197. DM 148.00. Springer-Verlag: London. 1988.

In this book, the first devoted entirely to PVR, the editors have assembled 27 papers dealing with the pathology, the management, and current research into this difficult condition. The material is presented under three main headings: an update, a discussion of common concerns, and reports of current clinical and research studies.

After an introductory overview of the general concepts of PVR there follows a number of clinical papers on the management of it in its increasing stages of complexity. These range from clinical and animal studies of the role of scleral buckling, and expansile gases without vitrectomy by Stanley Chang, to Zivojnovic's astounding collection of longstanding retinal detachments in severely traumatised eyes and their near miraculous recovery. The middle section is devoted to an almost verbatim transcript of a round table discussion by a number of well known experts in the vitreoretinal field. The last 17 articles range from a description of the organisation of the multicentre treatment trial which compares the use of silicone oil with that of expansile gases, to purely laboratory studies of drug delivery and the pharmacological manipulation of the cellular processes involved in the pathogenesis of PVR.

This book makes very interesting reading for those concerned in the management of patients with PVR. Being mostly a compilation of papers presented at the 1986 Academy Meeting, it suffers from a certain amount of repetition in the introductions and discussions in each paper. The 'current research studies' are by now over two years old, and much has happened since in the busy research on the intricacies of proliferative vitreoretinopathy.

Z J GREGOR

**Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine.** By David Regan. Pp 672. US$140·00. Elsevier: New York. 1989.

This is a single author textbook which is going to provide an important reference source for any electrodiagnostic clinic. Although the author writes from the point of view of the electronic engineer, his scope is wide. The book is in three sections. The first is divided into technical and mathematical considerations, the second is on basic research, and the third is on clinical applications. The main emphasis of the book concerns basic research and research techniques, and, although the clinical section is fairly short, it has been well written. The book is concerned with all forms of evoked potential, including visual, auditory, and somatosensory. The author is a well known authority in the field, and in this work his original textbook has been greatly expanded and updated. It will be welcomed by anyone concerned with the electrophysiology of the brain.

N R GALLOWAY

**Clinical Ophthalmology.** 2nd Edn. By Jack J Kanski. Pp 491. £75. Butterworths: Guildford, Surrey. 1989.

There is no better testimony to a successful book than the appearance of a second edition within five years after its original publication. In *Clinical Ophthalmology* Jack Kanski demonstrates the art of the master textbook writer: the text is well laid out, brief yet comprehensive. It covers all the important ophthalmic conditions, with the salient features of their clinical histories, physical signs, and management. Although the text is not referenced, there is an adequate list of suggested reading, which is as up to date as any newly published textbook can provide. The illustrations by Terry Tarrant are superb, and they admirably complement the wealth of colour photographs.

It is difficult to fault this excellent book. It has become the standard text for trainee ophthalmologists, both in Britain and elsewhere, and can also serve as a comprehensive reference book for practising ophthalmologists.

Z J GREGOR

**Diabetes and Its Ocular Complications.** By William E Benson, Gary C Brown, William Tasman. Pp 197. £40·50. Saunders: London. 1988.

This is a beautifully produced book which covers most clinical aspects of diabetic retinopathy. It also has chapters on pathology, together with four chapters on diabetic tissue damage and coagulation changes. There is a useful chapter on differential diagnosis of diabetic retinopathy. The book could be particularly useful to residents wanting to learn about this common condition, which is a major cause of blindness in the developed world.

But there are also many shortcomings. Papers are cited and reviewed without any criticism, and all statements made by different authors quoted are taken at face value, without any indication of which studies are based on too few patients or inadequate statistical analysis. Nor do the authors come up with definite suggestions or conclusion at the end of the chapters; this is most noticeable in chapter 14, on medical treatment of diabetic retinopathy.

A further shortcoming is that, when discussing pathogenic mechanisms, the authors do not mention the tremendous amount of work done in the field of cell culture. The papers quoted are extensive, but there are almost none from 1987 and few from 1986. Thus, although a new book, it is in the non-clinical aspects already out of date. This is really an indication of the rapid expansion of work in the field of retinopathy and the slow production of books.

While the book is a useful addition for residents, I do not think that it is of value to the researcher in the field of diabetic retinopathy.

E M KOHNER

**A Colour Atlas of Contact Lenses and Prosthetics.** 2nd Edn. By Montague Ruben. Pp 199. £35. Wolfe Medical: London, 1989.

This superb collection of illustrations covers a wide ranging though at times eclectic collection of topics on contact lenses. They demonstrate the author's breadth of expertise in many areas of contact lens practice, particularly in lens materials and design and in the fitting of the abnormal eye. The text is sometimes too concise to illuminate the understanding of the pedestrian reader, though the diagrams do much to overcome this. The book is an entertaining companion to more formal texts on contact lens practice.

JOHN DART

**Brain and Reading.** Eds. Curt von Euler, Ingvar Lundberg, Gunnar Lennerstrand. Pp 390. £50·00. Macmillan: Basingstoke, Hants. 1989.

The Rodin Remediation Conferences have acquired a reputation for excellent if occasionally eccentric meetings, in which a goodly collection of eminent speakers from a range of disciplines share the stage with a handful of more controversial and shadowy figures from the world of dyslexia research. In the early meetings there was a strong emphasis on visual factors, but this has progressively declined to the point where in these proceedings less than one-third of the papers are concerned with the visual system.

This is not a book for the novice. The papers do not follow a coherent theme, and the editorial contribution is largely confined to grouping together the papers under general topic headings. Thus within this text we are told both that dyslexia can arise from left hemisphere lesions (Aram *et al*) and that it is a consequence of right hemisphere dysfunction (Stein *et al*). The underlying basis of developmental dyslexia is postulated to be linguistic by many contributors (for example, A Liberman, I Liberman, Lundberg, Kean, Elbro) but visual by others (Stein *et al* Geiger, and Lettvin). It is regrettable that these contradictory claims are barely debated, leaving it mostly up to the reader to resolve the discrepancies, a hard job even for one well versed in the field. It would have been good to see someone from the 'language' camp discussing the 'visual' papers, and vice versa. The closest this book comes to addressing the crucial areas of disagreement is in a nicely argued review by Rayner, an eye movement specialist who accepts that there is good evidence for abnormal eye movements in dyslexics but argues that these are a consequence rather than a cause of reading problems.

Another difficulty for the non-expert to grapple with is the inclusion of several chapters that, on the face of it, appear to have little to do with dyslexia. The expert in reading disorders may be able to deduce the relevance of chapters on such topics as selective attention (Berlucchi *et al*), somatosensory cortex (Whitsel and Franzen), and motor control (Rothwell), but the non-specialist is given little help by either authors or editors in making the theoretical links.

There are, however, compensations. Rapid reproduction methods have made it possible for these proceedings to appear within a year of the conference, so that those chapters reporting recent research are fresh and topical. I was particularly interested in the report of neuroimaging techniques applied to children with developmental language disorders by Tallal and Katz, and in Gathercole and Baddeley's account of their recent research on development of phonological memory. Several of the other papers reviewing past as well as recent research provided valuable summaries of developments in a particular field. In this regard I found the paper by Sherman *et al* (on neuroanatomical anomalies in dyslexia), those by Fant and Lindblom (both dealing with aspects of phonetics), and the aforementioned paper by Rayner (on eye movements in dyslexia) especially useful.

The advent of desktop publishing systems with laser printers means that rapid reproduction is no longer synonymous with poor quality typescripts. However, it remains a costly process that results in a book that is priced so as to make most individual purchasers think twice.

Who, then, will buy this book? I suspect only a minority of readers of this journal will feel impelled to do so. For those with little specialist knowledge of reading, the wide range of unrelated papers can only be confusing. Those with a special interest in eye movement disturbances in dyslexia will find only four of the 29 chapters concerned with this issue, two of them arguing against the notion that visual abnormalities have a causal role. The four further chapters dealing with eye movements say little or nothing about dyslexia.

In sum, there is much excellent material in this book, but most of it demands a high level of background knowledge of the literature on reading disabilities to appreciate its significance.

DOROTHY BISHOP

# NOTES

### David Cole travel fellowship

The David Cole travel fellowship, instituted by Merck Sharp and Dohme in memory of Professor David Cole, will assist a visit to a hospital or research centre during the academic year starting 1 October 1990. The award will be equivalent to £2000. Its purpose is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

### Glaucoma Group research grant

The Glaucoma Group research grant, sponsored by the International Glaucoma Association, will be available for a research project clinically orientated to glaucoma for 1990. The award will be equivalent to £2000. The grant may be used towards salary or project expenses or for buying equipment. Both these awards are available to medical graduates and non-medical scientists resident in the United Kingdom or Irish Republic. They may be held concurrently with other awards. Further details and application forms are obtainable from Dr S Nagasubramanian, Secretary Glaucoma Group, Glaucoma Unit, Moorfields Eye Hospital, City Road, London EC1 2PD. The closing date for applications is 15 June 1990. The successful candidate will be informed by August 1990.

### Diabetic retinopathy

A workshop on 'Diabetic retinopathy: screening, assessment and treatment' will be held at the Hammersmith Hospital, London, on 8–10 October 1990. Its purpose is to establish a protocol for the screening of diabetic retinopathy and the minimal standard requirements for its management throughout Europe. The workshop has received the endorsement of the WHO/IDF Saint Vincent Declaration Working Group. It will be addressed to ophthalmologists and diabetologists with a specific interest and preferably experience in clinical retinopathy. The number attending will be limited to 50. Selections will be based on order of application, nomination to represent national associations, and country of origin, as the widest possible representation from all countries in Europe would be highly desirable. Further information from Dr M Porta MD and Dr E M Kohner, Diabetic Retinopathy Unit, Hammersmith Hospital, Du Cane Road, London W12 0NN.

### Ocular inflammation

The University of Alicante, Spain, and the Hadassah University, Israel, will sponsor the International Symposium on Ocular Inflammation in Alicante on 23–26 May 1990. The symposium will cover both clinical and research aspects of ocular inflammation and will include a basic sciences course. Call for free papers is open. Further information from Donoso Cortés, 73–1°, 28036 Madrid, Spain.

### Intraocular trauma

An Intraocular Trauma Course will be held on 1–3 October 1990 at Provinciehuis, Antwerp, Belgium. Further information from Mrs Dorine Verhoeven, Department of Ophthalmology, A Z Middelheim, Lindendreef 1, 2020 Antwerp, Belgium.

### IAPB Fourth General Assembly

The International Agency for the Prevention of Blindness (IAPB) will hold its Fourth General Assembly in Nairobi, Kenya, on 11–16 November 1990. The theme will be 'Sustainable strategies – agenda for the 1990s.' Those wishing to attend should register before 1 September 1990. They should send name, affiliation, address, telephone and fax numbers, and registration fee (payable to IAPB Kenya) to IAPB Coordinating Committee, c/o Ad-Venture Promotions Ltd, PO Box 11505, Nairobi, Kenya. The registration fee is US$175. The fee pays for attendance at the General Assembly, transport to and from the airport, lunches and teas each day, the opening reception, and the concluding banquet. Members should add US$15 for each guest they wish to bring to the reception and/or banquet.

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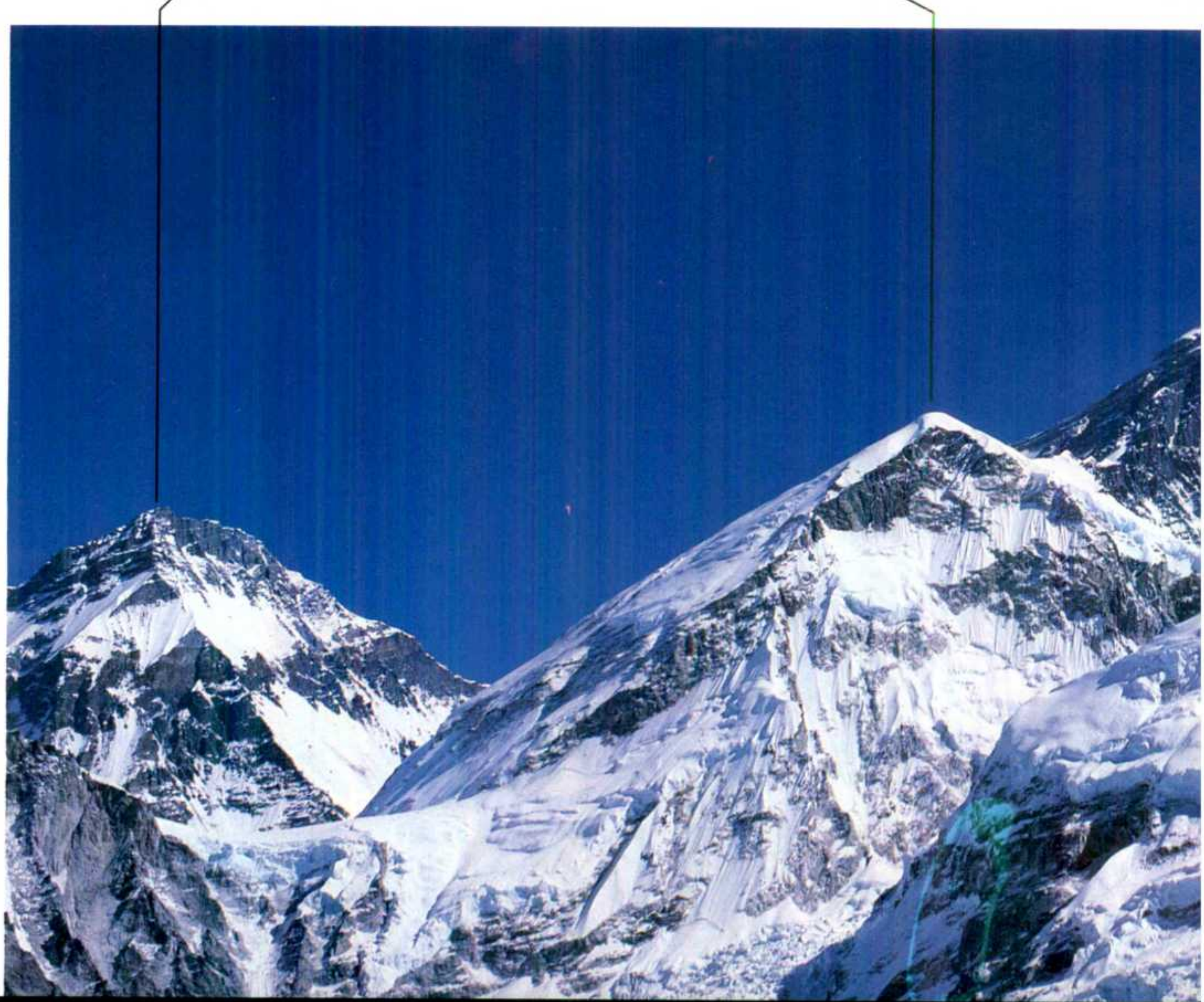

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use in children. *Nursing:* Mother should either st
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weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, bleph

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PATIENT DAYS
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keratitis, blepharoptosis, and decreased corneal
tivity. Visual disturbances, including refractory
ges (due sometimes to withdrawal of miotics),
pia, and ptosis.
ycardia, arrhythmia, hypotension, syncope,
t block, cerebrovascular accident, cerebral
emia, congestive heart failure, palpitation,
ac arrest.
chospasm (predominantly with pre-existing
chospastic disease), respiratory failure, dyspnoea.
lache, asthenia, nausea, dizziness, depression.
ersensitivity, rash, and urticaria.
tions with an unestablished relationship are
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**Reference**

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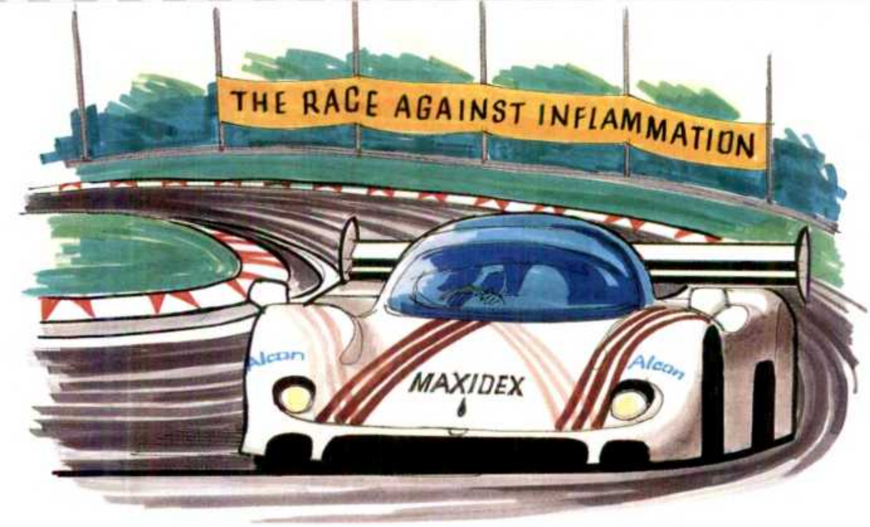

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*British Journal of Ophthalmology*, 1990, **74**, 257

BRITISH JOURNAL OF
OPHTHALMOLOGY

## *Editorial*

# How safe are intraocular lenses?

The general idea of the monthly editorial is to highlight a paper or papers. The choice of a paper on which to comment is not based on merit nor is it made as the result of putting the titles in a hat and drawing one out. The choice is rather a purely idiosyncratic one, the urge to comment on something that interests one personally, the desire to emphasise something which it is believed is not widely enough known, or the challenge of trying to understand something outside one's own special interests, and hence delving into literature not usually consulted.

This month's editorial is about the paper by Furuse and colleagues, which interested me, not because it reported world shattering discoveries but strangely enough because it discovered nothing. This is not supposed to be a disparaging remark; the paper is carefully researched and well presented but its results are negative. The negativity, however, refers to the stated object of the investigation, which was to discover if the corneal endothelium of diabetics fared worse than that of non-diabetics after intraocular lens (IOL) implantation. The investigation was successfully completed, and the result was that diabetes appeared to make no difference to the fate of the endothelium.

One might be tempted to conclude that no further information was likely to be gleaned from the paper, categorising it in the diabetic file as a negative finding. Such a dismissal would, however, be a mistake. Hidden in the paper is some information which in years to come could prove to be of importance. Those of us who saw the early results of IOLs were at first uneasy about the unacceptable number of cases of bullous keratopathy which occurred, leading some distinguished surgeons to abandon the operation and others not even to start it. We also know how, following the discovery of the vital role of the endothelium, bullous keratopathy became much less common, so that now the average surgeon and certainly the average patient normally take little notice of the possibility. We should ask ourselves if this is wise. Could it be that we are building up to a massive epidemic of bullous keratopathy in the future? Do we know enough about the natural history of the corneal endothelium to be confident that all is well and that we are safe to carry on implanting IOLs in all and sundry without a care in the world?

The present paper does not set out to evaluate the long-term prospects for endothelial survival after IOL implantation but only to compare diabetics with non-diabetics. Although the authors are encouraging about the probability of diabetes not being a risk factor for endothelial cell loss, their findings are not completely reassuring in this regard. There does appear to be a tendency for the diabetics to do a little worse, though the results do not achieve statistical significance. However, it must be pointed out that the numbers in the diabetic populations studied are rather small, arousing the suspicion that with larger numbers the results might not have been so reassuring. But this is pure speculation, and it would not be fair to question the present conclusions, which are justifiably made.

Leaving aside the question of the diabetics for the moment, we may consider the incidental finding that neither the diabetics nor the normal persons showed continued cell loss. This certainly gives grounds for a certain degree of optimism for the prospects of the world's huge and ever growing army of pseudophakes.

The authors point out that there have been mixed opinions on the chances of the endothelium of pseudophakes giving trouble in the distant future, some authors being optimistic but others pessimistic. Some of the reported studies are on the natural history of the endothelium, without pseudophakia, and even these do not altogether agree. For example, Laule and others[1] calculated that at the rate of endothelial cell loss found by them there would be no cells remaining by the age of 100 years, a daunting prospect for aspiring centenarians. But Wilson and Roper-Hall in 1982[2] found that, though there was a decline in the endothelial cell count up to the age of 50 years, there was no appreciable difference thereafter. The same authors also found[3] that approximately 17% of endothelial cells were lost after uncomplicated intracapsular cataract extraction with or without an IOL, but (not surprisingly) endothelial damage was far more serious if prolonged endothelial touch occurred. (The authors noted that the then little tried substance sodium hyaluronate showed promise.)

Substantial improvements in technique have been introduced in the last few years, not least the rapidly increasing use of sodium hyaluronate and other barrier substances, and it is becoming increasingly likely that the fears felt by many at the beginning of the decade that an epidemic of bullous keratopathy was on the way will prove to be unfounded. Certainly the present paper adds to the weight of evidence against the chances of such an epidemic.

REDMOND SMITH

1 Laule A, Cable MK, Hoffman CE, Hanna C. Endothelial cell population changes of human cornea during life. *Arch Ophthalmol* 1978; **96**: 2031–5.
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*British Journal of Ophthalmology*, 1990, 74, 258–260

## ORIGINAL ARTICLES

# Corneal endothelial changes after posterior chamber intraocular lens implantation in patients with or without diabetes mellitus

Nanako Furuse, Seiji Hayasaka, Yukari Yamamoto, Tomoichi Setogawa

## Abstract

**We examined 96 patients (111 eyes) who underwent extracapsular cataract extraction with the implantation of a posterior chamber intraocular lens. Of 96 patients 24 (29 eyes) with non-insulin-dependent diabetes mellitus had no or simple retinopathy; 72 patients (82 eyes) served as non-diabetic controls. The central corneas of all subjects were photographed by a specular microscope preoperatively and three, six, and 12 months postoperatively. No significant differences in the endothelial cell density, coefficient of variation, or cell loss were noted between diabetic patients and age matched non-diabetic subjects during the observation period.**

Extracapsular cataract extraction with the implantation of a posterior chamber intraocular lens provides excellent visual rehabilitation and has become the standard surgical approach. In the 1980s many patients with diabetes mellitus also underwent these procedures.[1]

Defects in corneal endothelial cells may occur with age,[2] but the mean cell counts appear not to decline after the age of 50 years.[3] Endothelial cell loss also occurs after intraocular lens implantation.[4-8] Some investigators indicated that the diabetic endothelium is morphologically abnormal and may be at risk in any intraocular surgical procedure,[9-11] while others showed no significant differences between diabetic and non-diabetic corneal endothelia.[12-14]

We therefore investigated whether or not the corneal endothelial cells after extracapsular cataract extraction with posterior chamber intraocular lens implantation in patients with diabetes mellitus differed from those in non-diabetic patients.

## Subjects and methods

### PATIENTS

We selected a total of 96 patients (111 eyes) who underwent extracapsular cataract extraction with posterior chamber intraocular lens implantation at Shimane Medical University Hospital between 1987 and 1988 and whose corneas were photographed by a specular microscope preoperatively and three, six, and 12 months postoperatively. The patients were classified as non-diabetic (72) and diabetic (24).

TABLE I *Distribution of patients and eyes in present study*

| *Group* | *Age (yr)* | *No. of patients (no. of eyes)*<br>*Non-diabetic* | *Diabetic* | *Total* |
|---|---|---|---|---|
| A | 52–59 | 12 (14) | 6 (7) | 18 (21) |
| B | 60–69 | 26 (27) | 7 (8) | 33 (35) |
| C | 70–79 | 34 (41) | 11 (14) | 45 (55) |
| A+B+C | | 72 (82) | 24 (29) | 96 (111) |

The diagnosis of diabetes mellitus was based on their blood glucose levels and the results of a glucose tolerance test in all subjects. The subjects were further divided into three groups according to age: group A, ages 52 to 59; group B, ages 60 to 69; and group C, ages 70 to 79 (Table I).

The 24 patients with non-insulin-dependent diabetes mellitus ranged in age from 52 to 79 years. The duration of diabetes mellitus in these patients ranged from two to 20 years: mean 8·9 (standard deviation 5·8 years). Their mean blood glucose level at the time of surgery was 7·5 (SD 1·6) mmol/l. Their haemoglobin A1 level was 9·9 (SD 1·8) g/dl. Six patients had been treated with diet only; 18 had been given oral drugs; and none was treated with insulin. Of 24 patients nine had no retinopathy and 15 had simple (background) retinopathy. None had been preoperatively treated with argon laser photocoagulation. Three, six, or 11 months after the cataract procedure and lens implantation seven patients with simple diabetic retinopathy received focal photocoagulation.

Excluded from the present study were those who wore contact lenses; patients with a previous history of ocular trauma or surgery, including preoperative photocoagulation; those with corneal disease, uveitis, glaucoma, and high myopia; and patients with operative and postoperative major complications such as posterior capsule thickening treated with neodymium: YAG laser.

### SURGICAL PROCEDURE

The preoperative examination of the patients included a complete ophthalmic history and examination, medical examination, axial length

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Accepted for publication 4 January 1990

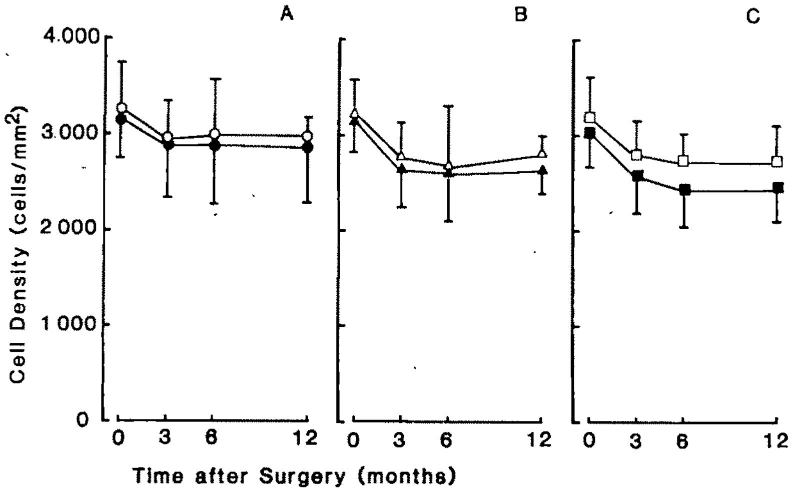

*Figure 1: Cell density (cells/mm²) in patient groups after surgery. Group A, ages 52 to 59; B, ages 60 to 69; and C, ages 70 to 79 years. ○, △, □, non-diabetics; ●, ▲, ■, diabetics. Means and standard deviations are shown.*

measurements of the eye, and corneal endothelial photographs.

Each surgeon operated on a similar percentage of patients in the non-diabetic and diabetic groups.

The following surgical technique was standard for all patients. A fornix-based conjunctival flap and a limbal incision were made, followed by an anterior capsulotomy with use of a bent 25-gauge needle. The nucleus was expressed, and cortical remnants were aspirated by means of an automated irrigation-aspiration instrument. After the capsular bag had been expanded with sodium hyaluronate instillation a modified C-loop or short C-loop posterior chamber intraocular lens was implanted in the capsule, sodium hyaluronate was aspirated, and an intracameral injection of acetylcholine was given. A peripheral iridectomy was made at the 11 or 1 o'clock position, and the wound was closed.

### SPECULAR MICROSCOPY AND ANALYSIS

All eyes underwent clinical specular microscopy (Konan Keeler). At least five photographs were taken of the central corneal endothelium in each eye to be operated on. The endothelial photographs were magnified to 155 times, and cell outlines were traced.

Quantitative analysis was performed by a computer assisted morphometric analyser. We determined the cell density, the coefficient of variation of cell size (calculated from the standard deviation per mean value: polymegathism quotient), and cell loss from the preoperative value. Statistical analysis was by Student's $t$ test. A probability of $p<0{\cdot}05$ was considered statistically significant.

## Results

The preoperative cell densities in the non-diabetic and diabetic subjects (Fig 1) were almost the same (about 3100 cells/mm²) in the three age groups. The cell densities decreased to 2600 from 2900 cells/mm² three months after the operation and remained unchanged thereafter in all groups. A statistical comparison is shown in Table II. No significant differences in cell density were found between non-diabetic and diabetic subjects.

The coefficient of variation for all subjects is shown in Figure 2. The preoperative values in non-diabetic and diabetic patients were almost the same (0·25 to 0·28) in all three age groups. No significant differences between non-diabetic and diabetic subjects were noted during the observation period (Table II).

10 to 20% of cells were lost during the three months after the operation (Fig 3), and the number of cells remained stationary thereafter. No significant differences in cell loss between non-diabetic and diabetic subjects were noted (Table II).

## Discussion

We could find no statistically significant differences in corneal endothelial changes after extracapsular cataract extraction with posterior

TABLE II *Statistical comparison of endothelial cell characteristics*

| | *p Value* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Group A (ages 52–59)* | | | | *Group B (ages 60–69)* | | | | *Group C (ages (70–79)* | | | |
| | *Before surgery* | *After surgery* | | | *Before surgery* | *After surgery* | | | *Before surgery* | *After surgery* | | |
| | | *3 mo* | *6 mo* | *12 mo* | | *3 mo* | *6 mo* | *12 mo* | | *3 mo* | *6 mo* | *12 mo* |
| Cell density | | | | | | | | | | | | |
| Non-diabetic *v* diabetic subjects | * | * | * | * | * | * | * | * | * | * | * | * |
| Non-diabetics | | | | | | | | | | | | |
| compared with preoperative value | – | ** | * | * | – | *** | *** | *** | – | *** | *** | *** |
| compared with 3-month value | – | – | * | * | – | – | * | * | – | – | * | * |
| Diabetics | | | | | | | | | | | | |
| compared with preoperative value | – | ** | * | * | – | ** | ** | *** | – | ** | *** | *** |
| compared with 3-month value | – | – | * | * | – | – | * | * | – | – | * | * |
| Coefficient of variation | | | | | | | | | | | | |
| Non-diabetic *v* diabetic subjects | * | * | * | * | * | * | * | * | * | * | * | * |
| Non-diabetics | | | | | | | | | | | | |
| compared with preoperative value | – | * | * | * | – | * | * | * | – | * | * | * |
| Diabetics | | | | | | | | | | | | |
| compared with preoperative value | – | * | * | * | – | * | * | * | – | * | * | * |
| Cell loss | | | | | | | | | | | | |
| Non-diabetic *v* diabetic subjects | – | * | * | * | – | * | * | * | – | * | * | * |
| Non-diabetics | | | | | | | | | | | | |
| compared with 3-month value | – | – | * | * | – | – | * | * | – | – | * | * |
| Diabetics | | | | | | | | | | | | |
| compared with 3-month value | – | – | * | * | – | – | * | * | – | – | * | * |

*p>0·05; **p<0·05; ***p<0·01.

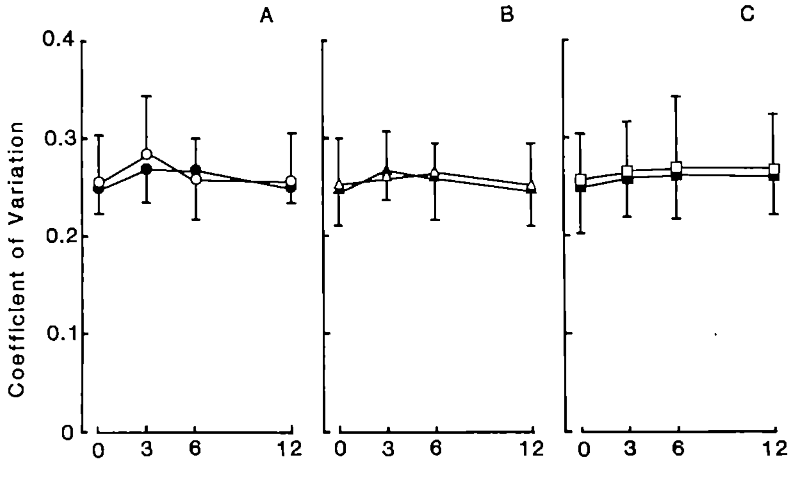

*Figure 2: Coefficient of variation in patient groups after surgery. See legend to Figure 1.*

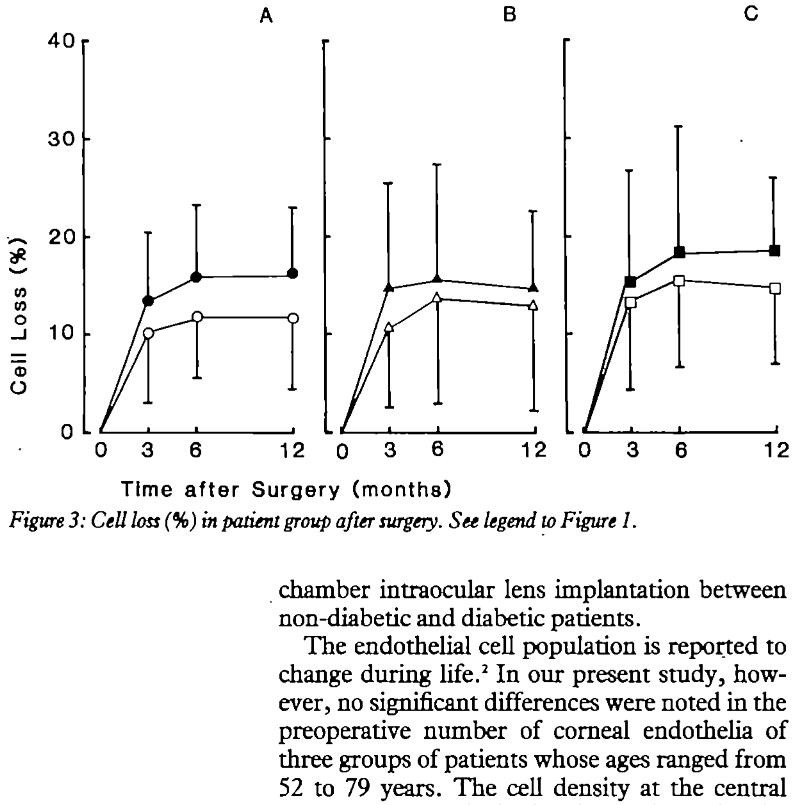

*Figure 3: Cell loss (%) in patient group after surgery. See legend to Figure 1.*

chamber intraocular lens implantation between non-diabetic and diabetic patients.

The endothelial cell population is reported to change during life.[2] In our present study, however, no significant differences were noted in the preoperative number of corneal endothelia of three groups of patients whose ages ranged from 52 to 79 years. The cell density at the central cornea preoperatively in the patients in the present study was about 3100 cells/mm$^2$. These values were slightly higher than those reported previously by other investigators.[4 6 7 9 10]

It has been suggested that mechanical trauma at the time of surgery is the main cause of endothelial cell loss, with later loss possibly caused by uveitis.[15] Schultz and associates[8] and Galin and coworkers[16] showed that central endothelial cell density stabilises approximately three months after uncomplicated intraocular surgery. Our results on the corneal endothelial changes following extracapsular cataract extraction with posterior chamber intraocular lens implantation were also similar to their findings.

Schultz *et al*,[9] Kamiya *et al*,[10] and Itoi *et al*[11] reported the increased coefficient of variation, or polymegathism, in diabetic endothelial cells. In our present study, however, no differences in coefficient of variation were noted between diabetic and non-diabetic eyes. Our findings were similar to those of Lass *et al*[13] and Shetlar *et al*,[14] who found no differences in coefficient of variation between diabetic and non-diabetic patients. Although the exact explanation for the discrepancy is difficult to determine, one possible reason may be that the difference in diabetic conditions, particularly blood glucose levels and duration of disease, were different in the patients among the various investigations. Another possibility may have been a damaging effect of photocoagulation on the corneal endothelium, though the effect is uncertain. We therefore excluded patients with a preoperative history of photocoagulation from the present study.

From our present findings we believe that all corneas in patients with diabetes may not be at risk in extracapsular cataract extraction with posterior chamber lens implantation.

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or twice daily. **PACK SIZE:** 5 ml plastic dropper bottles of 0.5% w/v solution. **BASIC NHS PRICE: £5.05**
26/0060. Full prescribing information is available on request.
man, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989; *96* (1): 8-11.
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Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

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PHARMACEUTICAL PRECAUTIONS

Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

LEGAL CATEGORY – POM

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Glauline is supplied as a sterile ophthalmic solution in a 5ml plastic dropper bottle.

FURTHER INFORMATION

Glauline has little or no effect on pupil size or accommodation. Glauline is generally well tolerated but some patients may complain of a slight stinging which soon passes off. Transient headaches have also been reported.

PRODUCT LICENCE NUMBERS

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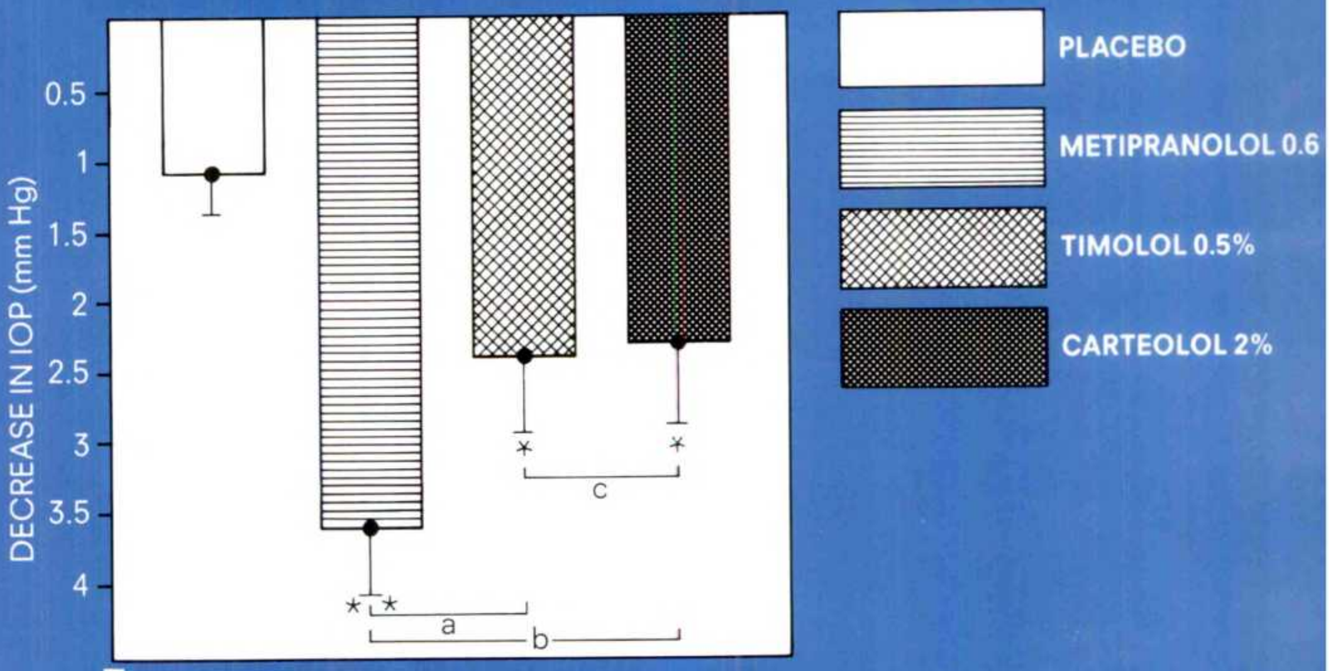
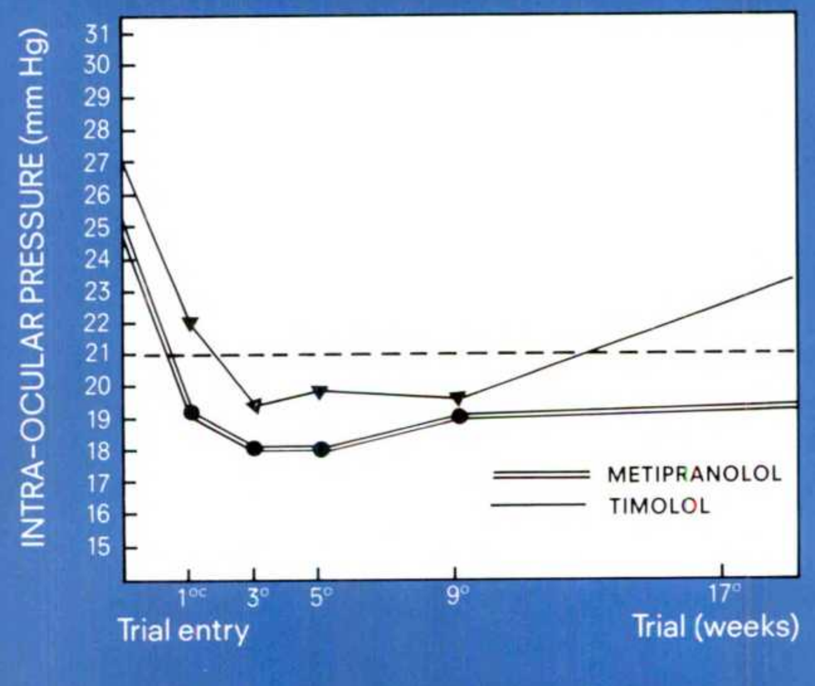
### (a) In a one drop study[1]



Mean (± SE) decrease in intra-ocular pressure *(IOP)* after one drop of ophthalmic ß-blocker in each eye. (*P < 0.01; **P < 0.001 vs. placebo; a, P < 0.01; b, P < 0.01; c, NS.)

### (b) In a middle term study[2]



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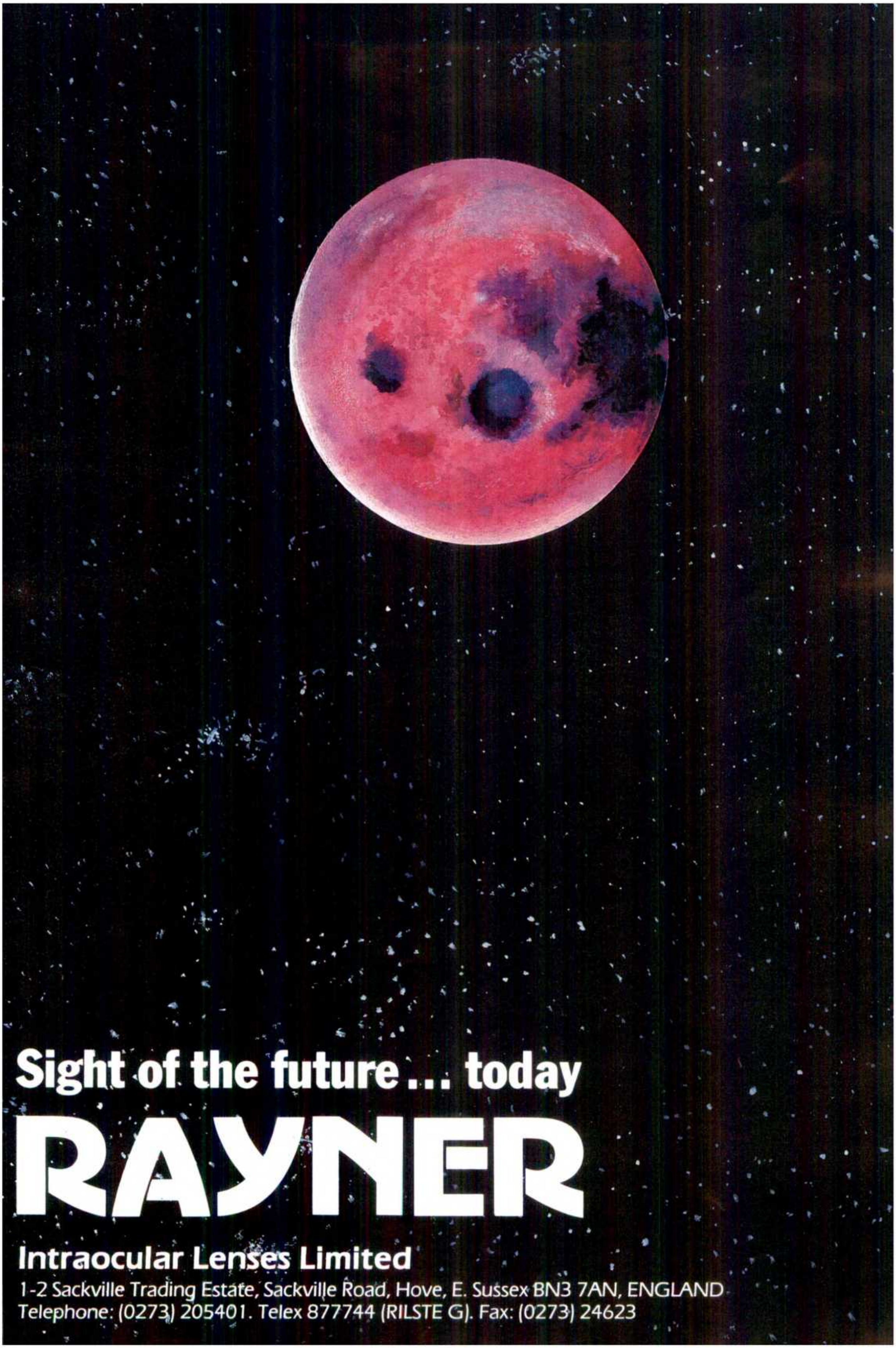

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# Manipulative damage to the endothelium of infant and adult donor corneas

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## Abstract

**Six human donor corneas were studied with the scanning electron microscope to quantify the hazards to the endothelium during the excision of corneoscleral buttons. Although the number studied was small, it was found that: (1) striae were more numerous in the flaccid, very young, donor corneas (under 1 year old) than in the more rigid adult corneas; (2) iridocorneal endothelial touch can result in loss of the posterior membrane and death of the touched endothelial cells. This corroborates the findings of other investigators. Both findings are important, because these conditions reduce the quality of the donor cornea for transplantation.**

The success of penetrating keratoplasty depends to a large extent on the donor corneal endothelium. This may be influenced by a number of factors including donor age, cause of death, technical handling, time from death to enucleation, and method and duration of storage.[1–6]

Modern preservation procedures involve the use of donor corneoscleral buttons. The extra handling for their excision puts the endothelium at risk of damage in addition to that due to post-mortem changes such as folding. Roozitalab and colleagues[5] have shown that excessive traction on the cornea during excision can result in the formation of stretch striae and that these represent damage to the endothelium. They have established an excision technique[7] which is currently recommended by the American Eye Bank Association. Grutzmacher *et al*[8] have compared the above recommended excision technique with another in which several donor eyes were incised in the sclera 1 mm from the limbus with the loss of the anterior chamber (AC). Their findings paralleled those of Roozitalab *et al.*[5] In addition they noted that striae were more frequent in young donors and in in-situ (globe retained in orbit) excisions. They suggested that this may be due to firmer attachments between the longitudinal ciliary muscles and the spur in the young, who incidentally represented the larger proportion of in-situ excisions.

Recently the protective effect of 1% sodium hyaluronate against endothelial cell damage from various types of trauma including stretching and rubbing of the cornea against other anterior ocular structures (iris, lens, anterior vitreous) was investigated in cats by Bahn *et al.*[9] They demonstrated small round areas of endothelial cell damage in corneas that were rubbed across the iris-lens surface. In contrast a cornea that was stretched by grasping Descemet's membrane showed large linear patterns of damage.

More recently Saggau *et al*[10] compared chondroitin sulphate corneal storage medium (CSM) and K-sol with regard to structural preservation of the endothelium by scanning electron microscopy (SEM). They found no consistent difference in the efficacy of corneal preservation between the two media. However, they observed large areas of endothelial cell disruption in the periphery of most of the corneas and speculated that this damage may be due to touch of the corneal endothelium by the iris.

Personal experience is that the young eye is in general more difficult to handle than the adult eye, that the cornea is more flaccid and prone to distortion and stria formation, and that the AC is relatively easy to lose, with consequent iridocorneal endothelial touch (ICET). It was felt that these factors also contribute to endothelial damage, and, since an increasing number of surgeons now employ infant donor corneas,[11 12] this study aimed to investigate their significance.

## Materials and methods

Six human donor eyes, one pair aged 8 months, one pair aged 62 years, one eye aged 3 months, and one aged 16 years (Table I) were used for this study. The ocular history was normal for all the donors. Each eye was examined with the slitlamp and the wide field specular microscope (the Pocklington, Keeler/Konan), particularly for the presence of striae and folds, before storage in a moist chamber at 4°C for 1–58 h. One eye (6 in Table I) was initially so stored for one and a half hours, then the cornea was excised and kept in McCarey-Kaufman (M-K) medium at 4°C for 120 h. The presence and intensity of posterior corneal rings (PCRs)[13 14] in the whole eyes were used as an indication of corneal rigidity. With sterile technique a corneoscleral button was prepared from each eye by making a scleral incision 2–3 mm posterior to the limbus into the suprachoroidal space with a no. 15 Bard-Parker blade. The incision was completed with curved corneal scissors and the ciliary body attachments to the scleral spur were separated. Care was taken to maintain the AC.[7] Because the eyes of the very young donors (1, 2, 3 in Table I) were too small to fit into currently available commercial eye stands, they were wrapped in gauze and hand held during corneal excision. Some difficulty was encountered in these cases during separation of the ciliary body from the scleral spur.

Under a dissecting microscope 0·1 ml of 2% glutaraldehyde solution was added to the aqueous humour by injection into the AC via the initial incision in eye 4. Care was taken not to touch the endothelium. The incision was com-

TABLE I *Donor information*

| *Eye* | *Age (yr)* | *Sex* | *COD* | *Death to enucleation* | *Enucleation to SL exam.** | *Time in MC at 4°C* | *Time in MK at 4°C* |
|---|---|---|---|---|---|---|---|
| 1 | 8/12 | M | Cot death | 7·75 h | 3 h | 21 h | — |
| 2 | 8/12 | M | Cot death | 8 h | 3·25 h | 21·25 h | — |
| 3 | 3/12 | F | Cot death | 4·16 h | 2 hr | 1·5 h | — |
| 4 | 62 | M | R arrest† | 25 min | 2·5 h | 58 h | — |
| 5 | 62 | M | R arrest† | 30 min | 3 h | 58·25 h | — |
| 6 | 16 | M | Suicide | 11 h | 1·5 h | 1·5 h | 120 h |

*Enucleation to slit-lamp examination. MC = moist chamber. MK = McCarey-Kaufman medium. COD = cause of death. †Respiratory arrest.

pleted with corneal scissors. The corneoscleral button (4 in Table I) was then placed without distortion into more glutaraldehyde solution and left for 2 h. 0·1 ml of aqueous humour was aspirated from the fellow eye (5 in Table I) in order to allow the corneal endothelium to touch the iris, and possibly the lens. After 1 minute the AC was reformed with 0·1 ml of 2% glutaraldehyde solution, and the cornea was excised and fixed as for eye 4. The fixed rigid button was easy to handle. The corneoscleral button of eye 6 was excised in the normal way[7,15] without prior fixation and was relatively difficult to handle. It was then fixed in glutaraldehyde for 2 h. All six corneoscleral buttons were prepared for scanning electron microscopy (SEM) as described elsewhere[16] and examined in a Hitachi S520 scanning electron microscope at 20 kV.

## Results

### CLINICAL OBSERVATIONS

Slit-lamp examination of the corneas of the six human donor eyes at the prestorage post-mortem times shown in Table I revealed minimal to moderate stromal oedema. Folds were obvious in the older corneas (4, 5, 6 in Table I) but none was seen in the very young. Subsequent slit-lamp examination at intervals during moist chamber storage showed a progressive increase in the haze of oedema in all the eyes and in the number of folds in the adults. Folding did not occur in the very young corneas.

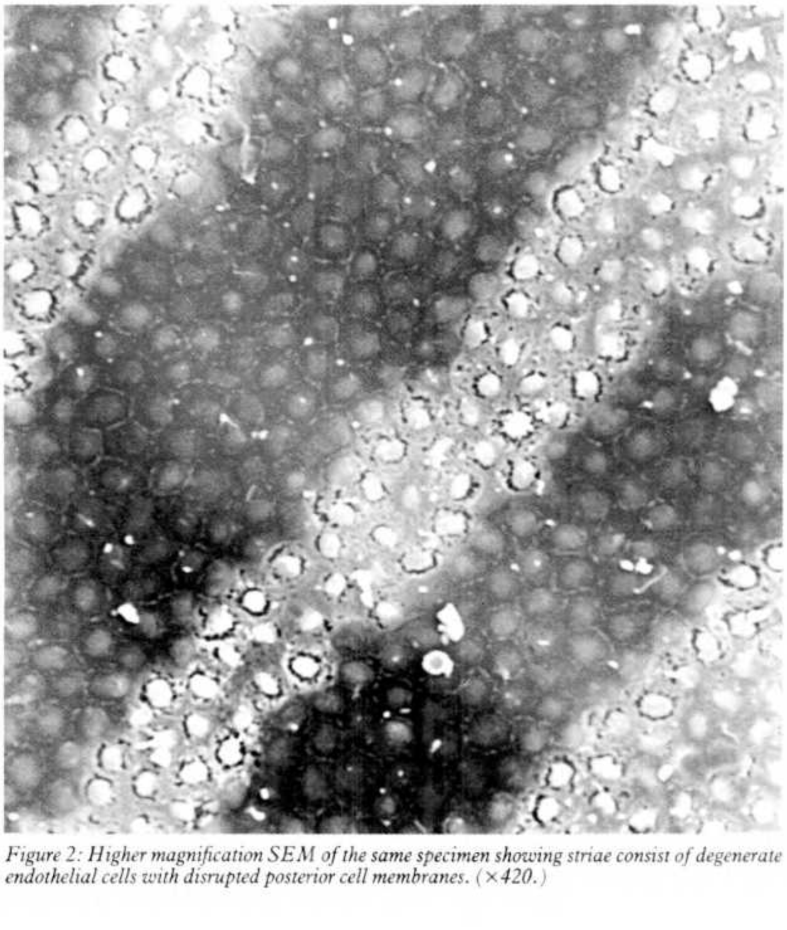

*Figure 2: Higher magnification SEM of the same specimen showing striae consist of degenerate endothelial cells with disrupted posterior cell membranes. (×420.)*

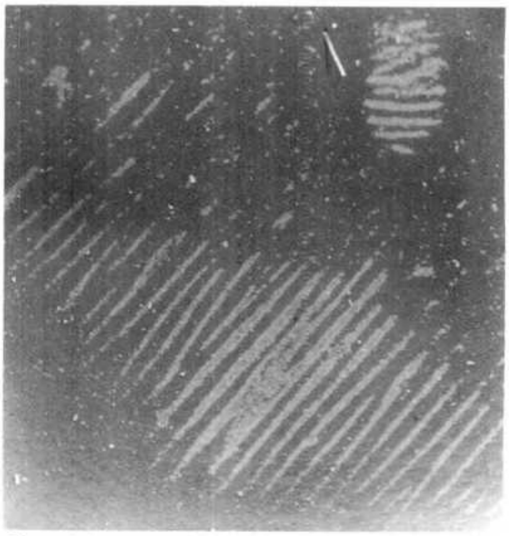

*Figure 1: Low power SEM of corneal endothelial striae in specimen 1. (×18.)*

A fairly adequate specular microscopical view was achieved in all whole eyes. The very young eyes (1, 2, 3 in Table I) showed a regular mosaic of small, rounded, similar cells with occasional 'dark areas' of about the same size as an endothelial cell. These possibly represented intracellular vacuoles or dead cells.[17] In specimens 4, 5, and 6 much of the endothelium was obscured by folds and oedema. Nevertheless, large areas of normal, polymegethous endothelium were seen. Posterior corneal rings, induced by applanation with the objective of the specular microscope, were distinct in the older corneas, unclear in specimen 6, and absent in the very young corneas. This indicates rigidity of the old and flaccidity of the young cornea.[13,14]

### OBSERVATIONS DURING EXCISION

Corneoscleral disc removal from the adult eyes was relatively easy because both hands were free to carry out the procedure, and the ciliary body was easy to separate from the scleral spur. It was more difficult in the very young because only one hand was free to effect the excision. This resulted in stretch and distortion of the corneas in eyes 1 and, to a less extent, 2, with partial loss of AC in 3 (Table I). Striae were obvious after excision in all the very young smooth corneas but were indistinguishable from folds in the adult corneas.

### SEM

Low magnification SEM revealed numerous greyish white parallel lines (Fig. 1) in the very young corneas (1, 2 and 3 in Table I). These were assumed to represent the striae induced during excision of the corneoscleral buttons. Higher magnification revealed that the lines consisted of rows of endothelial cells, 3–6 cells wide, whose nuclei were exposed by the loss of the posterior

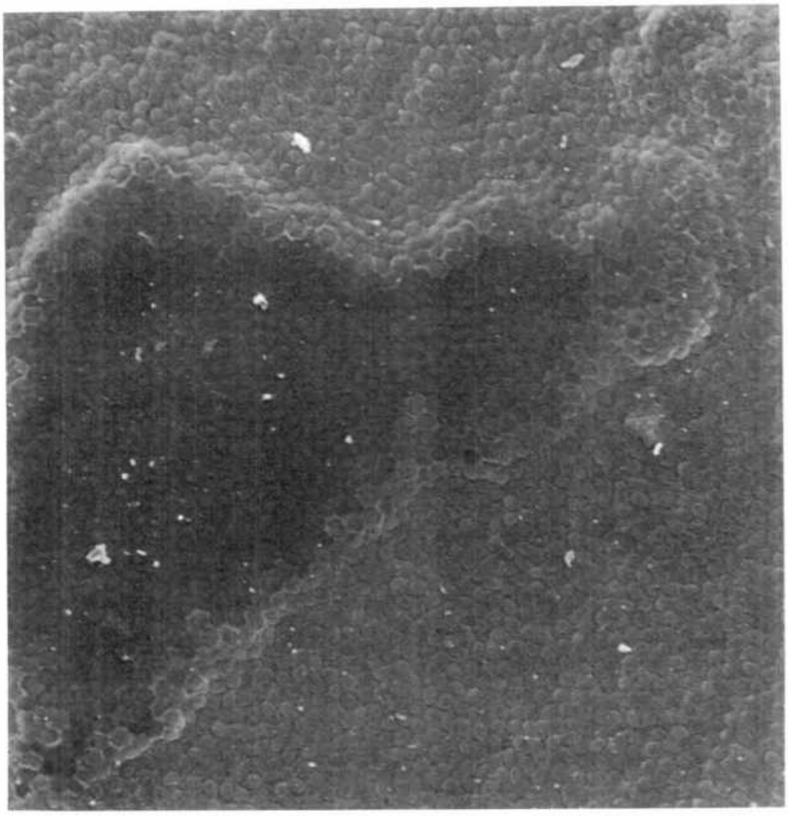

*Figure 3: Low power SEM of localised area of endothelium touched by iris in specimen 3. (×185.)*

cell membranes (Fig 2). Damage of this kind was more extensive in specimen 1 than in 2 – the fellow cornea – presumably because excision of the former was more difficult. The intervening endothelium appeared normal. In specimen 3 (Table I) low power SEM revealed dark patches with raised borders in the endothelium in addition to striae (Fig 3).

Higher magnification showed that in these patches the cells were altered as illustrated in Figure 4. Since the AC was partially lost in this specimen, it seems probable that the changes resulted from ICET.

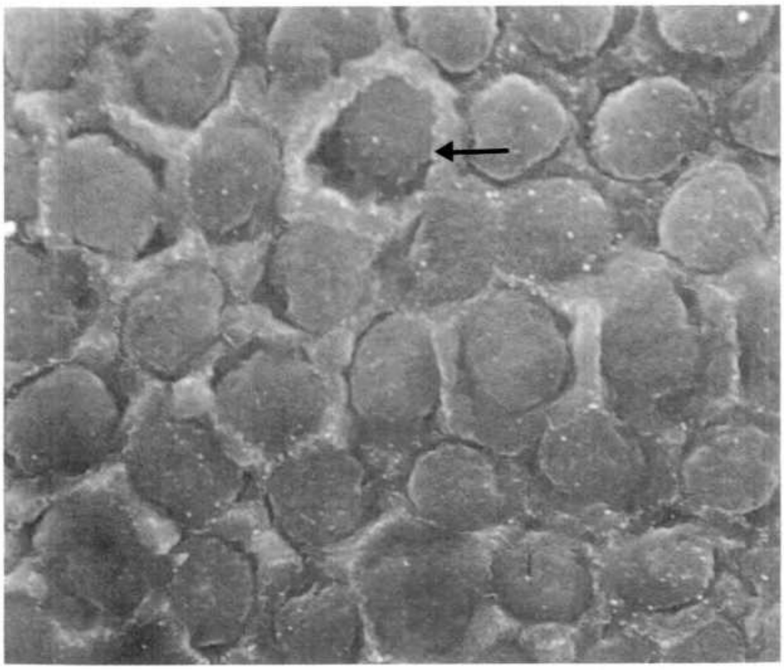

*Figure 4: Higher magnification SEM of localised area of endothelium touched by iris shown in Figure 3. Endothelial cells are present but a cell appears to have lost its posterior cell membrane (arrow). (×1200.)*

In specimen 4 (Table I) endothelial cell damage was mostly confined to folds, though there were a few peripheral striae. In the fellow cornea, specimen 5 (Table I) in which ICET was permitted, patches of similarly damaged cells were present in addition to those on the folds and of the striae. Although the 16-year-old cornea 6 (Table I) showed minimal traction damage, cell destruction was severe along the folds. It is noteworthy that in the adult corneas 4, 5, 6 in Table I the few striae crisscrossed with the folds. This confirmed that folds and striae are different entities, as previously noted.[16]

## Discussion

Damage to the donor corneal endothelium in the form of striae, best seen by retroillumination, has been reported by several investigators,[5 7 8 18] who have made suggestions as to their cause, significance, and prevention. However, there have been no discussions of their occurrence in the very young donor corneas which are becoming used more frequently.[11 12] Currently available commercial eye stands have been designed primarily to accommodate the eye of the adult donor. However, they can be modified to fit eyes of young donors – for example, by inverting the eye support of the Micra eye stand[15] over its distance piece. Alternatively, the young donor eye may be wrapped in gauze and hand held during the excision of the cornea. This increases the risk of damage to the corneal endothelium, which is already high owing to easy stretchability and distortion of the flaccid cornea, with loss of the AC and ICET.

Endothelial changes due to stretch have been demonstrated clinically[19 20] and experimentally.[8 9] In vivo, however, the changes are reversible and therefore of little consequence. Changes of similar appearance are induced by stretching in donor eyes. Here, in the in-vitro state they persist and so affect the quality of the graft material. The factors that cause striae, such as folding and stretching, occur at the time of enucleation and/or excision of the corneoscleral button, but the striae themselves may not become visible until much later.

In their comparison of excision techniques Grutzmacher *et al*[8] found that the number of striae correlated with the degree of stretch applied to the cornea, and that they were more numerous in young donors. This they considered was because many of them were excised in situ (globe retained in orbit). These authors did not state whether infant donors were included in their series; and the four cases reported by Roozitalab *et al*[5] were of adult donors. It seemed reasonable to assume, however, that the great flaccidity of the young cornea allows greater distortion and therefore stria formation. Indeed, in the present study the very young donors showed more traction damage especially, in 1 (Table I, Fig 2), and to a less extent in 2 and 3 (Table I) than in the adults; and all excisions were ex situ. Since we had only three infant corneas to study, it is difficult to draw

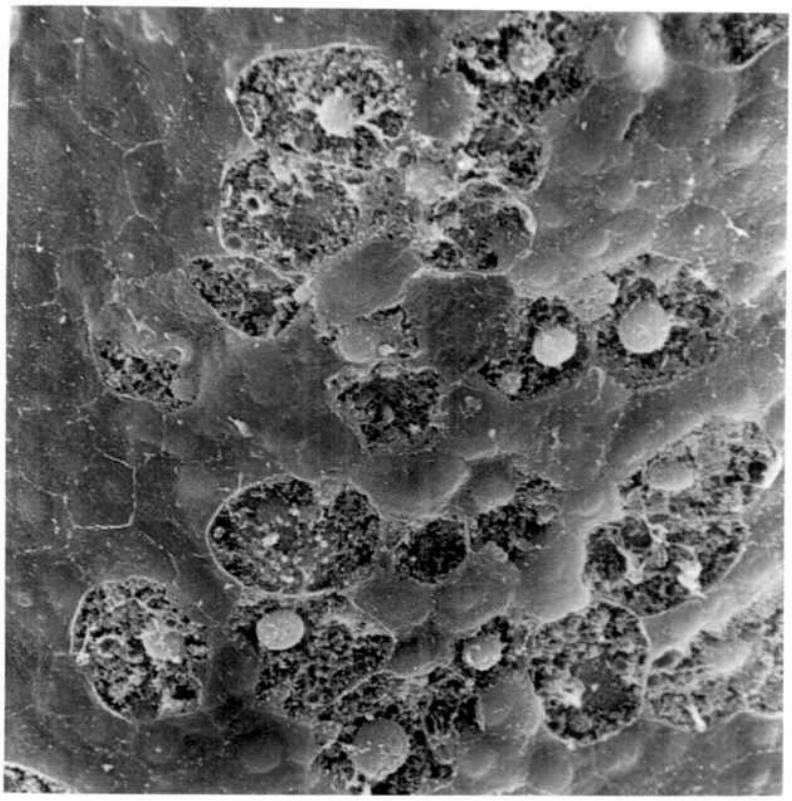

*Figure 5: SEM of adult donor cornea showing endothelial cells damaged by iris touch. (×725.)*

valid conclusions as to whether or not infant corneas are more susceptible to stria formation because of their flaccidity than the more rigid adult cornea.

Polack[21] showed that contact between the human endothelium and iris caused damage to the former. In the present study damage as seen by SEM similar to that found by Polack was noted in specimen 5 in which the AC was partially lost (Fig 5). Undoubtedly this resulted from ICET as in Polack's case, and confirms our suspicion and that of Saggau *et al.*[10]

Although our numbers are small, this and other studies[5 8 9] show that excessive traction of the cornea and ICET can result in damage to a significant number of endothelial cells which is irreversible in the in-vitro, donor, state.

This damage reduces the quality of the donor cornea and should be avoided.

It is proposed that donor material, especially the very young, be used fresh when possible to eliminate one excision procedure. If the cornea must be stored, extreme care should be taken during excision to avoid AC loss and excessive traction. From the observations of McCrae *et al*[22] and Bahn *et al*[9] it would appear that the use of a viscoelastic substance such as methylcellulose to prevent contact between the endothelium and iris would be useful. Furthermore, it is clearly desirable that stored corneoscleral buttons be examined immediately before their use for penetrating keratoplasty in order to eliminate those with excessive striae.

If the use of infant donor corneas for transplantation is to be encouraged, it would be desirable to have the appropriate instruments for their handling. Developing an eye holder suitable for infant donors would be a major first step to reducing the number of striae and overcoming the difficulties encountered during the excision of corneoscleral buttons. This is now under investigation.

The authors wish to thank Miss E Bennett for typing the manuscript, Dr W Ng for expert technical assistance, and the Department of Medical Illustration for the photographic processing.

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# Simultaneous pterygium and intraocular surgery

Brendan I Ibechukwu

**Abstract**

**Fifteen patients were treated with simultaneous pterygium and intraocular surgery. Eleven of them had pterygium excision with cataract extraction, while four had pterygium excision with trabeculectomy. There was no evidence of increased risk of pterygium recurrence or of complications following cataract operation or trabeculectomy as a result of the combined procedure. In an environment where pterygium is endemic and medical facilities inadequate a combined procedure is recommended to save time and cost.**

Pterygium is a major ophthalmic problem in Jos, Northern Nigeria. It commonly occurs in eyes with surgically treatable intraocular conditions such as cataract and glaucoma. The definitive treatment of pterygium is its removal which can be done prior to or combined with most intraocular operations. A simultaneous operation for excision of pterygium and treatment of cataract or glaucoma, when possible, is simple. The techniques are presented and discussed here.

## Simultaneous pterygium excision and cataract extraction

The commonest site of a pterygium is nasal, but occasionally both nasal and temporal pterygia occur in the same eye with cataract. The surgical procedure up to excision of the pterygium is the same no matter whether the pterygium is nasal, temporal, or both, or whether the cataract extraction is intra- or extracapsular.

A conjunctival incision is made 5 mm from the limbus and is continued through the pterygium nasally or temporally or both depending on the site of the pterygium. The conjunctival flap is reflected as usual towards the cornea throughout the extent of the incision to expose the limbus. The proximal conjunctiva in the area of the pterygium is undermined and all subconjunctival pterygium tissue carefully excised. All blood vessels are cauterised. Radial incisions are made above and below the neck of the pterygium isolating it from the rest of the conjunctival flap. The head of the pterygium is then removed by a superficial keratectomy.

A corneoscleral incision is then developed to the size appropriate for either intra- or extracapsular cataract extraction. After removal of the cataractous lens, the corneoscleral wound is closed with interrupted 8-0 virgin silk sutures. If the corneoscleral incision extends into the pterygium area, the sutures are inserted closer together there.

After the anterior chamber is reformed, the conjunctival flap is replaced and closed with interrupted 8-0 virgin silk leaving a 3–4 mm bare sclera in the region of the pterygium. Atropine 1% and chloramphenicol 0·5% drops are instilled into the conjunctival sac, and a pad and bandage are applied. Postoperative medications are as for ordinary cataract extraction.

## Simultaneous pterygium excision and trabeculectomy

Most of our glaucoma patients also have pterygia. Whenever trabeculectomy is indicated, I excise the pterygium at the same time if present. A limbus-based conjunctival flap is again adopted. The conjunctival incision is continued through the pterygium.

After the sclera is cleared, the site of the trabeculectomy is centred and demarcated with cautery at 11 o'clock for a nasal pterygium, at 1 o'clock for a temporal pterygium, and at 12 o'clock where nasal and temporal pterygia occur together. Blood vessels in the pterygium area are cauterised.

The neck of the pterygium is isolated from the rest of the conjunctival flap with radial incisions at its upper and lower borders. Removal of the pterygium is then completed with a superficial keratectomy.

Superficial and deep scleral trabeculectomy flaps are now developed and the trabeculectomy operation is carried out. After Tenon's capsule has been restored, the conjunctiva over the trabeculectomy is closed with continuous 5-0 catgut. The conjunctival margins bordering the area of the pterygium are sutured to the sclera with close, interrupted 8-0 virgin silk sutures. Cyclopentolate 1% and chloramphenicol 0·5% drops are instilled into the conjunctival cul-de-sac and pad and bandage applied. Postoperative management is as for ordinary trabeculectomy.

## Discussion

Jos University Teaching Hospital (JUTH) has a catchment area spanning four states of Nigeria where pterygium has a high frequency. Pterygium takes a significant proportion of our clinic and theatre times. For instance, in the 12 months July 1987 to June 1988 pterygium accounted for 10·6% of all operations in the eye theatre. In the following 12 months, July 1988 to June 1989, it accounted for 9·4% (Table). These figures are comparable with the overall incidence of the disease as noted by Cameron[1] and Youngson[2] but higher than that noted by Nworah.[3]

*Incidence of pterygium in Jos University Teaching Hospital eye theatre*

| | *Total no. of operations* | *No. of pterygia excised* | *Pterygium as % of total no. of operations* |
|---|---|---|---|
| July 1987–June 1988 | 625 | 66 | 10·6 |
| July 1988–June 1989 | 692 | 65 | 9·4 |

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Combined pterygium excision and cataract extraction or trabeculectomy as described above has some obvious advantages for both the hospital and the patient. It shortens the waiting list and theatre time. It cuts down costs for the patient through a unified operation charge and fewer hospital visits.

The indications for simultaneous operation include all those for cataract or glaucoma surgery plus those for pterygium excision. In this centre we are in complete agreement with Boruchoff and Foulks[4] on the major indications for removal of a pterygium. These include a significantly inflamed eye resistant to topical medications; relentless progression of the pterygium towards the visual axis with associated corneal astigmatism, both of which impair vision; and the physical appearance of an eye that is cosmetically unacceptable to the patient. Simultaneous operations should be done on quiet eyes selected for elective surgery rather than on inflamed eyes and eyes suffering from injury or acute glaucoma.

The occurrence of pterygium with cataract creates some additional optical problems. Tight closure of the cataract wound and pterygium both create a with-the-rule astigmatism wound closure by steepening the vertical meridian and pterygium by flattening the 180° axis.[5] Whereas the astigmatism induced by tight wound closure can be reduced by removing the offending stitches postoperatively, the pterygium induced astigmatism can be eliminated only by careful excision of the pterygium. If the pterygium is not removed during the cataract operation, it can create such a degree of postcataract astigmatism that the visual result may be very poor.[5]

The following points in the surgical techniques should be noted:

In both procedures, the pterygium excision is completed before the eye is opened. Keratectomy is difficult in a soft eye.

During the cataract wound closure corneoscleral sutures are inserted closer together within the bare sclera area to compensate for the loss of conjuctival protection.

In the combined pterygium excision and trabeculectomy, decentring of the trabeculectomy site in nasal or temporal pterygium plus the additional virgin silk sutures round the bare sclera both prevent excessive drainage.

## Complications

There have been no specific complications attributable to the simultaneous procedures other than those postoperative problems associated with cataract extraction, trabeculectomy, or pterygium excision. The keratectomy sites have healed within our normal five-day postoperative inpatient period. No recurrence of pterygium has been recorded in the 15 patients (16 eyes) operated on and followed up so far. There has been no aqueous leakage from the trabeculectomy or cataract wounds despite the deficient conjunctival protection in the pterygium sites.

Four of the patients who had combined operations had trabeculectomies for open-angle glaucoma, while 11 had cataract extractions. Their pterygia were among 86 excised by the author during the 24 months July 1987 to June 1989. One of the patients had bilateral nasotemporal pterygia with mature cataracts. He had simultaneous pterygium excision and cataract extraction in both eyes.

One puzzling complication of pterygium operation is the high rate of recurrence of pterygium. This is borne out by the extreme diversity of surgical techniques and medical adjuvants which have been used for its treatment. At this centre we use the 'bare sclera' technique, cautery, and one or other postoperative medication. Of the 86 eyes that had pterygium excision, only 60 returned for the accepted three-month minimum follow-up.[6] Overall there have been 23 recurrences, giving a recurrence rate of 38%. Youngson,[2] who used a similar technique in Jerusalem, reported a recurrence rate of 37%. Different recurrence rates have been reported in the literature. This may be due to lack of uniformity in the duration of follow-up, as the interval between treatment and recurrence varies considerably. For example, within the first three months, only nine recurrences (15%) were detected. The number rose to 15 (25%) within six months and to 20 (33·3%) in 12 months. The true recurrence rate is therefore more likely to be between 30 and 40%.

## Conclusion

In our environment pterygium occurs in most patients requiring intraocular surgery. I advocate that whenever there is no contraindication the pterygium should be removed just before the eye is opened for the intraocular operation. The simultaneous procedure is beneficial to both the hospital and the patient and makes for a better visual prognosis in patients undergoing cataract extraction.

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# The lens after renal transplantation

G Adrien Shun-Shin, Peter Ratcliffe, Anthony J Bron, Nicholas P Brown, John M Sparrow

## Abstract

**A single masked observer examined 55 non-diabetic patients chosen randomly from a population of patients who had undergone renal transplant. The mean age was 41 years and mean time from transplant was 4·4 years (1–10 years). Fourteen patients were found to have a posterior subcapsular cataract (PSC). The axial thickness of the right lens of the renal transplant population, even in the presence of a PSC, was significantly larger than in a control population of 99 patients with clear lenses. The PSC of renal transplantation is readily distinguished from age related PSC because the opacity lies in the superficial cortex at a depth proportional to time from transplant and the lens maintains a normal anterior clear zone. It is proposed that this type of cataract be called 'recovering' PSC. It is concluded that the cataractogenic insult occurs mainly during the peritransplant period. Maintenance doses of immunosuppressives or steroids are therefore probably not cataractogenic.**

Black *et al* were the first to point out the association of cataract and systemic steroid therapy in their study of patients with rheumatoid arthritis.[1] This association has been recently reviewed by Urban and Cotlier.[2]

There is good evidence on biochemical[3 4] and epidemiological[5-7] grounds to associate cataract with renal failure. It has been calculated that the relative risk for cataract in renal failure is 12·4.[7]

Several studies have looked at the prevalence of posterior subcapsular cataract (PSC) in renal transplant patients. The reported prevalence pooled from 12 other studies[8-19] involving 709 patients is 51%. These studies have attempted to relate dose, duration, and total amount of steroid given to the renal transplant patient with the prevalence of PSC, but the results have not been clear cut.

The aim of this study was to characterise clinically the salient features of PSC in renal transplantation (RT-PSC) and to compare them with age related posterior subcapsular cataracts. A further aim was to study the relationship of renal transplant posterior subcapsular cataract to various postulated cataractogenic factors. It has been shown that age related PSC lenses are smaller than normal.[20] Therefore our third aim was to study the thickness of the lens of renal transplant patients in order to study the effect of transplantation on lens size.

## Materials and methods

Fifty five patients who had undergone renal transplantation between nine months and 10 years previously were studied. All patients were examined by one ophthalmologist (GASS) who was masked as to the renal status of the patient.

Selection criteria for the renal transplant population were as follows. Patients were excluded if they had had more than one transplant, were aged 56 years or more, were diabetic, or had Alport's syndrome. Patients with congenital or traumatic cataracts were also excluded. The purpose of the upper age limit was to minimise confusion between renal transplant and age related PSC.

### PATIENT GROUPING

Patients were grouped according to the different treatment protocols which have evolved over the years. These treatment protocols used at the Renal Unit, Churchill Hospital, Oxford, are summarised as follows:

*Group A.* Between January 1978 and October 1979 all transplant patients were randomised either to a high dose steroid group (4125 mg of prednisolone over the first 90 days) or low dose steroid group (2544 mg of prednisolone over the first 90 days).[21] Nine patients from each group were selected at random by means of random number tables for the lens study.

*Group B.* Between January 1980 and December 1984 all transplant patients were randomised to receive either low dose prednisolone (2175 mg of prednisolone for the first 90 days) and azathioprine or alternatively only cyclosporin for the first three months. After three months all the patients were treated with prednisolone and azathioprine.[22] All patients with rejection episodes were treated with boluses of 0·5 g of methylprednisolone. Patients have therefore been further subdivided into those receiving less than 3·0 g and 3.0 g or more of methylprednisolone.

Thus four groups of six patients were chosen by means of random number tables.

*Group C.* The current regimen for renal transplant patients from January 1985 is known as triple therapy. This consists of cyclosporin 4·0 mg/kg/day, azathioprine 1·5 mg/kg/day, and prednisolone 20 mg/day.[23] A total of 13 patients were chosen at random by random number tables from this group.

As regards the ophthalmic examination of the renal transplant population, all the patients were refracted. Visual acuity was measured by the log MAR Ferris chart.[24] Pupils were then dilated with tropicamide 1% drops and phenylephrine 10% drops repeated at least twice in order to produce a pupil diameter of at least 7 mm. The lenses were examined at the slit-lamp and graded by the Oxford clinical cataract classification and grading system.[25] The lenses were photographed with the Brown Scheimpflug slit image camera[26] and the Oxford retroillumination camera (High Tech Vision).[27] Funduscopy was performed. The cup/disc ratio was recorded, intraocular

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pressures were measured by aplanation tonometry, and all glaucoma suspects had a Friedmann field examination performed.

### SELECTION OF CONTROLS

Staff and relatives of patients, with no known history of significant ocular pathology attending the Oxford Eye Hospital were recruited to the control group. The exclusion criteria included known diabetes, diabetes diagnosed from a random blood test using a reflectance meter, known renal failure, and known ocular pathology such as glaucoma or uveitis. All patients were dilated with tropicamide 1% drops and phenylephrine 10% drops, repeated at least twice until a pupil diameter of at least 7 mm was obtained. Only clear lenses were photographed on the Scheimpflug camera. Our definition of a clear control lens was: no posterior subcapsular cataract, no spoke opacity, normal (grade 3) anterior clear zone, nuclear brunescence (grade 1), and white scatter (grade 1) as defined by the Oxford clinical cataract classification and grading system.[25]

A total of 99 right eyes were deemed suitable for the study. The age of controls ranged from 13 to 82 years.

### AXIAL THICKNESS MEASUREMENTS

The axial thickness of the right lens of the renal transplant population and the controls was measured from the Scheimpflug negatives by image analysis using the Modular Cataract Image Analysis System (Pipistrel PLC) (Sparrow JM, *et al*, unpublished data).

### PATIENT DATA

The daily dose of prednisolone, the cumulative dose of methylprednisolone, and the total dose of steroid at one week. one month, and six months after transplantation and at the time of ophthalmic examination was obtained from the notes. The daily dose of azathioprine and cyclosporin A at the same four time intervals was also recorded.

The blood levels of the following electrolytes at those four time intervals were obtained from the notes: glucose, sodium, potassium, urea, creatinine, and calcium. A note was also made of whether the patient had been prescribed any diuretic or calcium antagonist in the preceding period at one week, one month, and six months and at the time of ophthalmic examination.

## Results

Fifty five renal transplant patients aged between 21 and 55 were seen. Twelve had bilateral PSC and two had a unilateral PSC affecting the right eye only. One patient was diagnosed as having ocular hypertension. No patient had any field loss detected on the Friedmann field.

### ANALYSIS OF RENAL TRANSPLANT SUBGROUP

The effect of possible cataractogenic factors acting in the peritransplant period was sought. Unpaired *t* tests were performed, and there was no statistically significant ($p>0{\cdot}05$) relationship between the daily dose of prednisolone, the cumulative dose of methylprednisolone, and the cumulative dose of steroids and the presence of PSC at the four time intervals defined previously. Similarly there was no demonstrable relationship between the daily dose of azathioprine and cyclosporin A at any of the four time intervals and the presence of PSC in the right eye. We also failed to find any significant association between the levels of electrolytes mentioned previously and PSC ($p>0{\cdot}05$).

A $\chi^2$ test was performed on the data for diuretics and calcium antagonists. Here again no statistically significant relationship was found at any of the four time intervals ($p>0{\cdot}05$). As regards lens biometry in renal transplant patients and controls: the axial lens thickness of controls was plotted against age. The correlation coefficient was 0·852. The axial lens thickness increased linearly with age and the equation representing the regression line is

$$t=0{\cdot}02576\times A+3{\cdot}350,$$

where t is the thickness of the lens in millimetres and A is the patient's age in years.

This compares with

$$t=0{\cdot}0235\times A+3{\cdot}34$$

from Weekers *et al*[28] for 150 controls.

Figure 1 is a plot of axial lens thickness of the renal transplant population versus age of patient at time of examination. The interrupted line represents the regression line for controls and the solid line represents the regression line for the renal transplant population. The correlation coefficient is 0·752. The corresponding equation is

$$t=0{\cdot}0349\times A+3{\cdot}17$$

It is seen that most data points lie above the dotted line representing the regression line for the control population. Linear regression analysis in groups (analysis of variance) confirms this impression. There is a powerful main effect ($p=6{\cdot}26\times10^{-6}$) such that lenses of renal transplant patients are on average larger than those of controls after age has been accounted for. There is

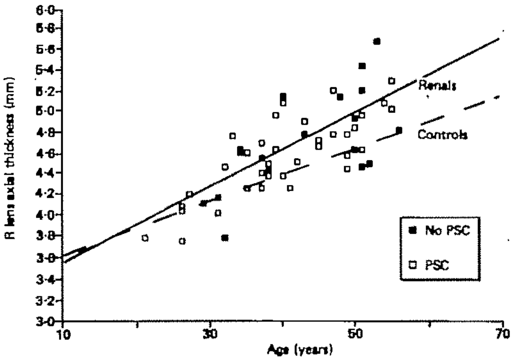

*Figure 1: Right axial lens thickness (mm) plotted against age of patient (years). Each square represents the right eye of a renal transplant patient. Shaded squares are those with PSC and unshaded squares those without PSC. The interrupted line represents the regression line for the 99 control right eyes, and the uninterrupted line represents the regression line for the 55 right eyes of the renal transplant population.*

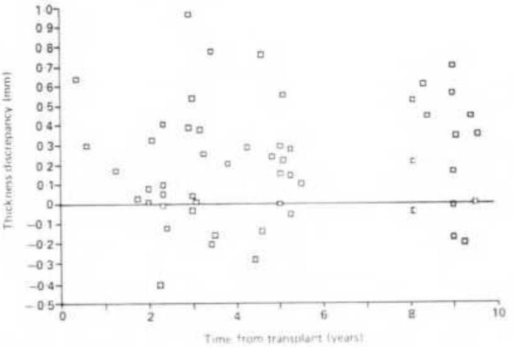

*Figure 2: Thickness discrepancy (mm) plotted against time from transplant (years). Thickness discrepancy = true thickness of lens minus the expected thickness of a control lens matched for age.*

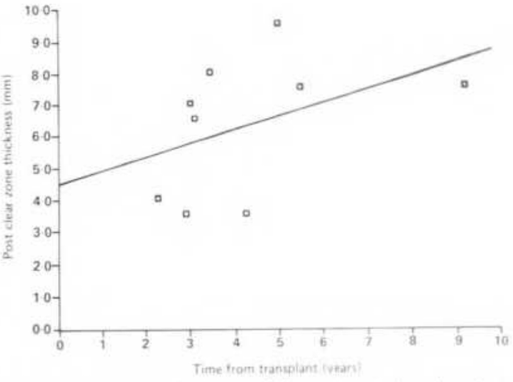

*Figure 3: Posterior clear zone thickness (mm) plotted against time from transplant (years): r = 0·55.*

in addition an interaction (p = 0·021) between age and renal transplant status such that the slope of the regression line against age in renal transplant patients is steeper than that of controls.

In Figure 1 the shaded squares represent lenses with PSC and the unshaded squares the clear lenses. The axial thickness of the right lens – with or without cataract – of the renal transplant population is thus significantly larger than a control population.

Figure 2 is a scattergram of the discrepancy in lens thickness of renal transplant patients versus controls plotted against the age of the transplant. Discrepancy = true thickness of the lens minus expected thickness of a control lens corrected for the same age derived from the control regression line.

There was no demonstrable relationship between increase in size of lens and time from transplant. The anterior clear zone of the lens was not reduced in any of the 26 lenses with a posterior subcapsular cataract as judged from standard photographs from the Oxford clinical cataract and grading system.[25] All anterior clear zones were graded three (normal).

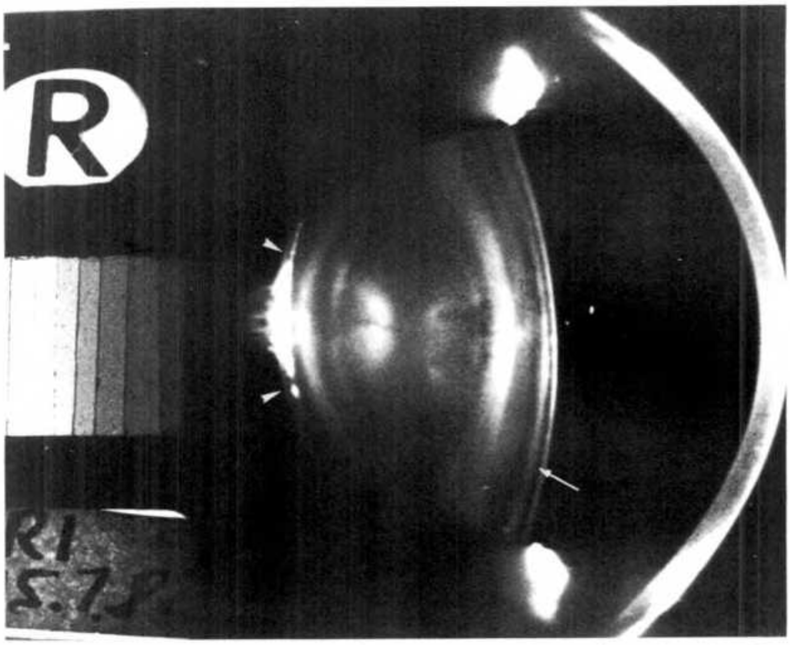

*Figure 4: Scheimpflug of a 'recovering' PSC taken nine years after renal transplantation. Note the normal anterior clear zone (arrow) and the PSC which lies away from the posterior capsule (arrow heads).*

In nine patients with a PSC it was seen that the PSC did not in fact lie against the posterior capsule but that a zone of optically clear fibres separated the PSC from the posterior capsule. The axial thickness of this zone was measured and plotted against time from transplant in Figure 3. A regression line is drawn. The correlation coefficient is 0·55. The graph shows a tendency for the PSC to lie deeper within the superficial cortex with time. There was no relationship between the grade of PSC and the total amount of steroid given.

In spite of the PSC the reduction in vision was small. The range of recorded LogMAR acuity[24] was 0·40 to −0·1 (6/15 to 6/4·5) in those with PSC.

## Discussion

### MORPHOLOGY OF PSC

The lens grows in thickness throughout life.[29] New fibres are continually added to its surface. These fibres are then in turn covered by a newer layer of fibres as further fibres are added. Biomicroscopy of the normal lens shows an anterior clear zone. (ACZ), also known as C1α, immediately deep to the anterior capsule. This zone is the most recently formed fibres and measures approximately 125 μm in width in vivo; it represents two to three years of growth.

The morphology of the PSC in renal transplantation is interesting. No narrowing of the anterior clear zone (arrowed in Figure 4) was noted even in the patients with PSC seen as early as 21 months and 25 months after surgery. This contrasts with the situation in age related PSC, where the ACZ is consistently reduced or absent.[20] The inference is that there is little or no disturbance of new fibre formation and differentiation in the renal transplant patients.

There is a further difference between age related PSC and RT related PSC. A zone of clear fibres can be seen superficial to the PSC in renal transplantation (as shown in Figure 4) but not in age related PSC. This movement inwards of the PSC is analogous to that seen in radiation induced PSC[30] and in lamellar cataracts.[11] Radiation results in a temporary halting of epithelial mitosis, and the re-establishment of mitosis at first results in abnormal fibres in a posterior subcapsular location followed by normal fibres which separate the opacity from the capsule. In lamellar cataracts the opacity appears to 'sink' into the lens as new fibres are added superficial to it.

The size of this zone of clear fibres increases with time from transplant, as shown by Figure 3. The low correlation coefficient of $r=0{\cdot}55$ is probably due to technical difficulties in measuring the size of this zone of clear new fibres: the distances to be measured are small, and it is difficult to decide where the posterior capsule and the PSC lie owing to the amount of forward and backward scatter from the PSC.

It is therefore suggested that in RT PSC, where the ACZ is of normal thickness and the PSC lies deep to a layer of optically clear fibres, the lens has recovered from the cataractogenic stimulus. This concept of a 'recovering' lens implies that the cataractogenic stimulus is no longer acting and therefore that the stimulus was of limited duration acting during the peritransplant period. It is concluded that maintenance doses of immunosuppressives are not cataractogenic. In contrast, in age related PSC, the lens is 'failing': the lens is smaller and the ACZ is reduced or absent.

It is to be noted that the incidence of PSC was relatively low in our group; 12 out of 55 patients (22%) had a PSC in at least one eye compared with 51% from a pooled series of 12 studies.[8–19] This could in part be due to the fact that in our study patients with Alport's syndrome or diabetes were excluded.

## AXIAL LENS THICKNESS

In this study the lens axial thickness in the transplant patients was statistically greater for age than normal lenses whether or not a PSC was present. This is reminiscent of the increased thickness of non-cataractous diabetic lenses reported by Brown *et al.*[31] and recently for type I diabetics, in whom it has been shown to be related to the duration of diabetes.[32]

Steroids have been shown to increase lens cell permeability in vitro.[33] It could therefore be hypothesised that increased lens thickness in post-transplant patients is due to an effect on lens permeability. An alternative hypothesis is increased lens growth. Activity of the Na$^+$-proton antiport system, which is thought to exist in the lens (Duncan G, personal communication), is coupled in some cell systems to second messenger systems concerned with cell volume regulation and cell growth. The renal hypertrophy which accompanies diabetes mellitus has been attributed to stimulation of the Na$^+$-proton antiport system.[34 35] In *x* ray cataract the period of mitotic inhibition immediately following exposure is followed by a mitotic spurt above baseline level.[36] A similar mechanism could theoretically produce increase lens size in the renal transplant population.

In this study increased lens thickness was noted even in those patients who developed PSC. This is in contrast to age related PSC, where lens size is small for age,[20] presumably owing to a reduction in the formation and differentiation of normal lens fibres. The probable explanation for this difference is that there is a limited period in the transplant patients during which cataract is formed, following which normal fibres are laid down outside the posterior subcapsular opacity.

## CONCLUSIONS

It has been shown in the group of patients studied that renal transplantation and its associated therapeutic regimen is associated with the development of PSC in 22%. This PSC is thought to be formed in the peritransplant period. In the groups studied the PSC does not progress, but in time it is followed by the formation of normal clear fibres superficial to the opacity. It is proposed to call this type of PSC a 'recovering' PSC to distinguish it from age related PSC.

This study was supported in part by the generosity of the Royal National Institute for the Blind. We thank Professor P J Morris for permission to recruit his patients to the study.

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# Persistently raised intraocular pressure following extracapsular cataract extraction

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## Abstract

**In this population based study we have reviewed the files of all patients who underwent an extracapsular cataract extraction (ECCE) between 1984 and 1987, were normotensives prior to surgery, and were followed up for at least 10 months after the ECCE. From a total of 1047 operations 746 qualified for the inclusion criteria; of these, 16 (2·1%) were found to have a consistently raised intraocular pressure (>21 mmHg) on more than two occasions) at four months or later after surgery and throughout at least a six-month period. An increased incidence of secondary aphakic glaucoma was associated with anterior chamber IOL implantation ($p<0·001$) and posterior capsule rupture ($p<0·01$), but not with any of the other variables examined (age, sex, surgeon).**

Increased intraocular pressure (IOP) is a well recognised late complication after cataract surgery even in patients who were normotensive before the operation. In most cases the postoperative pressure increase is benign and transient and appears in the early postoperative period. In some cases, however, the IOP elevation occurs several weeks or even months after the cataract operation. It does not affect the non-operated eye, remains constantly high, and the patient often needs pressure lowering medication. In other cases the early postoperative increase in IOP is not transient but remains constantly high, and again treatment is frequently warranted. Both these types of cases used to be called aphakic glaucoma (or pseudophakic, if the condition occurred in the presence of an intraocular lens (IOL).

The term 'aphakic glaucoma' has been discontinued because a variety of different conditions have been included under this name. For the same reasons we prefer the term 'persistently elevated IOP', but for the purpose of this study, the shorter name 'secondary aphakic glaucoma (SAG)' has been used. Little information could be found in the literature as to the incidence of SAG. The available reports indicate incidence rates varying between 1 and 7%.[1-5] These wide variations are due to the diversity of the surgical procedures (intra- or extracapsular) employed in each study and the variety of the intraocular lenses used by the different authors – anterior chamber (AC), iris plane (IP), or posterior chamber (PC). The differences may also be caused by the varying numbers of cases in each study – 100[1] to 2382[4] – or the extent of the follow-up. Furthermore, some of the studies date back to the days when the microscope was not the standard for cataract surgery, and also the methods of study were other than those used today.

Owing to the need for an epidemiological study of the incidence of SAG we undertook to review our data derived from a series of patients who underwent ECCE during a given time in the Negev region of southern Israel.

## Material and methods

A population based study could be undertaken in the southern district of Israel, where the Soroka Medical Center has the only available surgical facilities for performing cataract surgery and all follow-up care is performed by staff of the University Department of Ophthalmology in the various out-patients clinics and with easily traceable records. The files of 1040 adult patients who underwent ECCE between 1 July 1984 and 31 December 1987 were reviewed.

*Exclusion criteria – general:* Known increased IOP or pressure-lowering medication before the cataract surgery; age less than 36 years; past history or evidence of uveitis on examination; past history or evidence of trauma on ocular examination; past history or ocular evidence of angle closure or treatment for such; insufficient information on follow-up (patient moved, deceased, etc.)

*Exclusion criteria – postoperative:* The fellow (non-operated) eye also developed increased IOP during the follow-up period; the operated eye suffered after ECCE a retinal vein occlusion, vitreous haemorrhage, or developed proliferative vitreoretinopathy (PVR).

After some cases had been excluded according to these criteria we were left with 659 patients (746 eyes) who were followed up for at least 10 months after surgery. For each case, the following data were recorded: age, sex, whether an intraocular lens (IOL) was implanted at the time of surgery, if posterior capsule rupture occurred at the time of surgery, and whether anterior vitrectomy was performed. In cases where an IOL was implanted the type of lens (posterior chamber or anterior chamber – PC/AC) was also recorded, as was capsulotomy when it was performed at a later stage with the YAG laser. The data were submitted for statistical analysis and the significance was calculated by the $\chi^2$ method.

### SURGICAL TECHNIQUE

The cataract surgery was performed whenever possible under retrobulbar anaesthesia. The surgeons included all staff members from residents in training to senior faculty.

The conjunctival flap was fornix-based. Viscoelastic material was always used, both during the anterior capsulotomy and the IOL insertion.

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Phakoemulsification was not used, and the nucleus was expressed manually. The irrigation/aspiration was also performed manually, by the closed chamber technique with the AC maintainer. Whenever possible, a PC IOL was implanted, aiming for 'in the bag' placement. The types of PC IOLs preferred varied throughout the study period, but the majority of PC lenses used were the modified J-loop type, initially with prolene and later polymethyl methacrylate (PMMA) loops, a 6 mm optic in the first two years and 7 mm after that, with mixed straight or 10° angulated loops.

Whenever an AC IOL had to be inserted because of an opened vitreous face, the choice of IOL throughout the study was the 6 mm, three loops Dubroff type lens (manufactured by Ophthec BV, Groningen, Holland). The operative wound was closed with separate 9:0 virgin silk sutures and the Healonid removed from the AC at the end of the operation. Postoperative care included a topical steroid/antiobiotic compound, given four times a day for three to four weeks after surgery.

### DEFINITIONS OF CRITERIA

Patients were considered to have SAG whenever at least three IOP readings of 22 mmHg or more were recorded in the period starting at least two months after the cataract operation and during a follow-up period of not less than six months. Patients receiving pressure lowering medication and whose IOP in this postoperative period was lower than 22 mmHg owing to the treatment were also included. Their ages ranged from 36 to 94, mean of 69·1 (SD 9·3) years. There were 348 women and 311 men, and the mean follow-up time was 19·7 months (range 10–42). Among the 659 patients were 87 bilateral cases.

The list of IOLs used for the 746 eyes is as follows: PC 553 (74·2%), AC 50 (6·7%), no IOL 143 (19·1%).

The posterior capsule was inadvertently opened at the time of surgery in 66 eyes. In 16 of these cases a PC IOL was implanted, but in the other 50 eyes the remaining capsule was not considered sufficient to support a PC lens and an AC IOL was inserted. All cases with vitreous presentation during surgery underwent an anterior vitrectomy.

Secondary capsular opacification was noted in 89 eyes, for which YAG capsulotomy was performed at various times after ECCE.

## Results

A persistently increased IOP or SAG was found in 16 eyes (2·1%) of 14 patients (2·1%). A very high incidence of SAG was encountered in the eyes of patients with an AC IOL: 6 patients out of 48 (12·5%) or 7/50 eyes (14%). This was significantly different from the incidence of the condition in patients with PC IOLs – 7/468 (1·5%) (553 eyes) ($p<0{\cdot}001$) and from those patients in which no IOL was implanted 1/143 (0·7%) ($p<0{\cdot}001$) (Table I).

There was also a strong correlation between the surgical opening of the posterior capsule and SAG: an increased IOP was found in 7 patients out of 60 (12·6%), in which the posterior capsule was opened at surgery (8/66 eyes = 12·1%) and in only 1 of the 71 patients (1·4%) (89 eyes) in which the PC was opened by YAG laser at a later stage. This difference was significant too ($p<0{\cdot}05$).

Of the 87 patients with bilateral ECCE one developed SAG in both eyes. This was a patient with high myopia; the surgery itself was uneventful and no IOL was implanted.

The mean age of the 14 patients with SAG was 71·2 (SD 6·8) years and the two sexes were equally represented (seven men and seven women). An attempt to match SAG to the surgeon performing the operation indicated a similar distribution of cases among the surgeons.

## Discussion

The incidence of SAG in the present study is comparable and within the range reported in the literature. However, unlike previous reports this study is, to the best of our knowledge, the first population based study to include all ECCE operations performed and followed up in order to detect SAG and to recognise those factors which may increase the risk of this condition.

Our results indicate that the only strongly associated factors for SAG were the surgical opening of the posterior capsule, with consequent anterior vitrectomy and the implantation of an AC IOL. As previously mentioned, in 66 eyes the posterior capsule was inadvertently opened during surgery; in 8 of these eyes (7 with AC IOL and 1 with PC IOL) a late persistent increase in IOP developed (12·1%). The risk of the same developing in the remaining 680 eyes with intact posterior capsule was only 1·17%. Furthermore, one cannot ignore the fact that the two eyes with SAG without IOL were those in one patient with bilateral ECCE. This bilateral IOP increase may represent not two independent events but the time related pressure increase occurring in some patients. If this case is eliminated, the risk of SAG with intact posterior capsule drops to 1·0%.

In an attempt to elucidate the separate roles of these two factors 27 secondary AC IOL implantations which were performed during the study period on patients with the same inclusion criteria were analysed. In 13 of these eyes the vitreous face remained intact, while in 14 an anterior vitrectomy was also performed prior to the implantation of the Dubroff type of AC IOL. None of the 27 eyes developed SAG.

It therefore remains doubtful which factor is the main culprit in the mechanism which leads to a raised IOP after ECCE. Nevertheless, it appears that the low incidence (1·17%) of SAG following uncomplicated ECCE is further proof that cataract surgery, as performed today, is a safe procedure with little likelihood of SAG developing. Intraoperative complications, how-

TABLE I *Incidence of increased IOP after ECCE according to IOL types*

| | | | |
|---|---|---|---|
| AC IOL | 7/50 | (14%) | |
| PC IOL | 7/553 | (1·3%) | $p<001$ |
| No IOL | 2/143 | (1·4%) | $p<001$ |

AC = anterior chamber. PC = posterior chamber.

ever, significantly increase the incidence of a persistently increased IOP.

This paper has been presented in part at the ARVO Meeting, Sarasota, Florida, May 1989.

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# Computer assisted analysis of fluorescein videoangiograms

Paul A R Meyer, Fred W Fitzke

Abstract

**The efficient analysis of fluorescein videoangiograms requires immediate access to any frame in a video sequence and complete control over the time base during replay. It should also be possible to compare any two frames by rapid subtraction or to subtract any phase of the study from the remaining sequence. A program that performs all these tasks has been written for a low priced desk-top microcomputer. This should facilitate the clinical introduction of fluorescein videoangiography.**

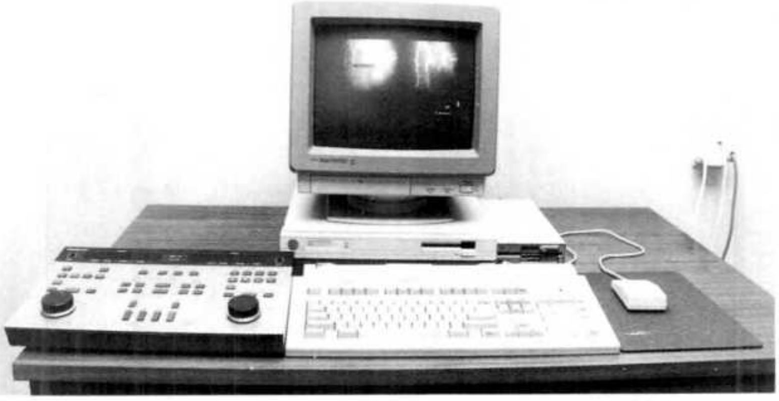

*Figure 1: The Archimedes computer with mouse (right) and video controller (left). Images are presented in quarter screen format.*

Fluorescein videoangiography, during which fields are captured every 0·02 second, records the dynamics of vascular perfusion as well as its anatomy.[1-4] In the episcleral circulation this has clarified the distinction between arteries and veins.[4] It has also revealed interarterial communications and confirmed that anterior ciliary arteries may carry blood away from the limbus.[4 5] However, clinical fundus and anterior segment videoangiography have never become widely established.

The spatial resolution of the best video cameras is lower than that achieved by photography, and this is further reduced by all but the most expensive recording systems. However, the major hindrance to clinical videoangiography has been the difficulty of interpreting video images. When an ophthalmologist reads a photographic angiogram he examines each part of the sequence at a different rate, sometimes repeatedly roving forwards and backwards in time. This is a function that most video recorders perform very poorly.

The system that is presented here uses a fast desk top microcomputer to give the observer instant access to any location in an angiographic sequence and complete control of the rate at which images are displayed. Any two fields may be compared by the use of subtraction.

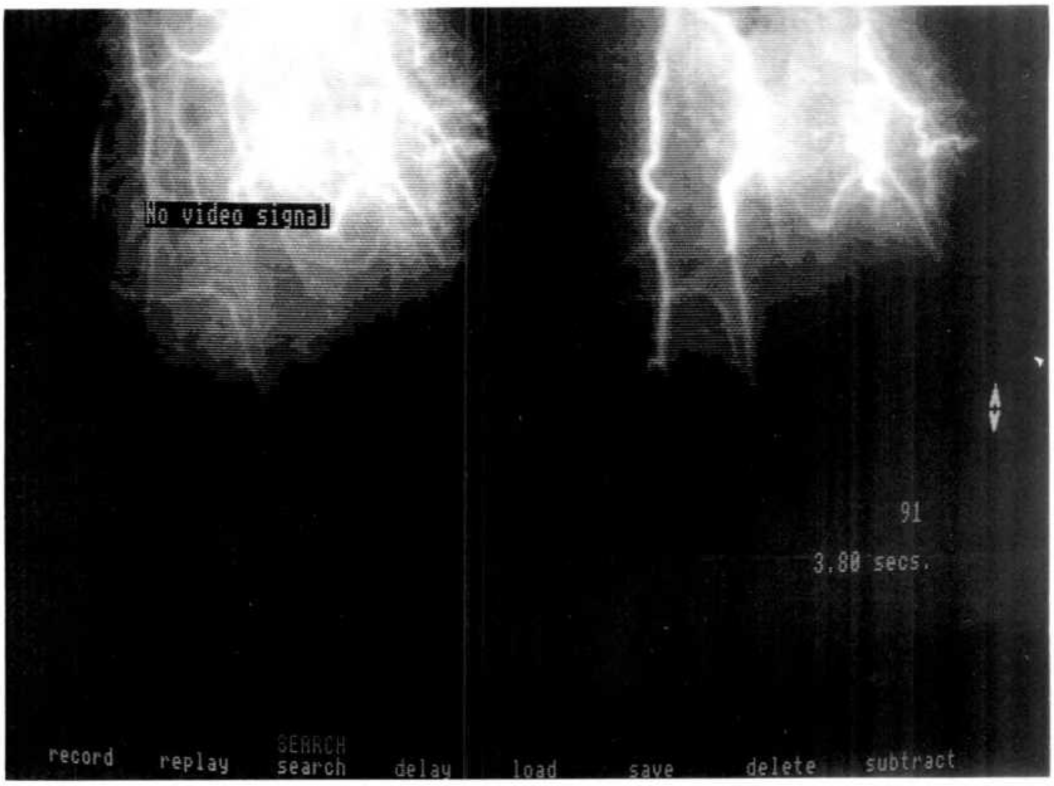

*Figure 2: Standard screen format during 'search' routine. Left: most recent line image. Right: selected RAM image. Menu (bottom line) is always present and accessible by mouse.*

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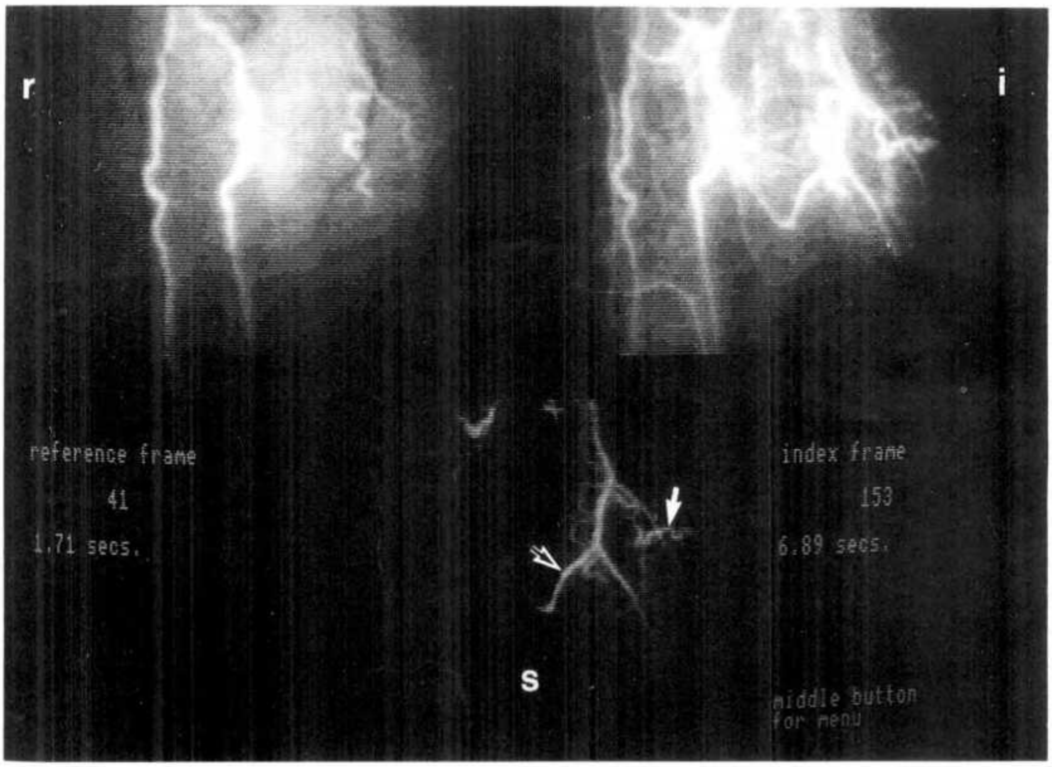

*Figure 3A*

*Figure 3: Subtraction: Index frame* (i). *Reference frame* (r). *Subtracted image* (s).

*A: Arterial phase subtracted from late venous phase. In this example arteries with delayed perfusion (closed arrow) and veins (open arrow) are demonstrated.*

## Methods and results

HARDWARE

The image analysis system is based on the Archimedes 440 computer (Acorn, Cambridge). This is equipped with 4-megabytes RAM and a 20-megabyte hard disc. A video digitiser and frame store 'podule' (Watford Electronics) is also required (Fig 1).

Low-dose anterior segment fluorescein videoangiograms were recorded on to U-matic videotape by an image intensified Nuvicon camera, as described previously.[4]

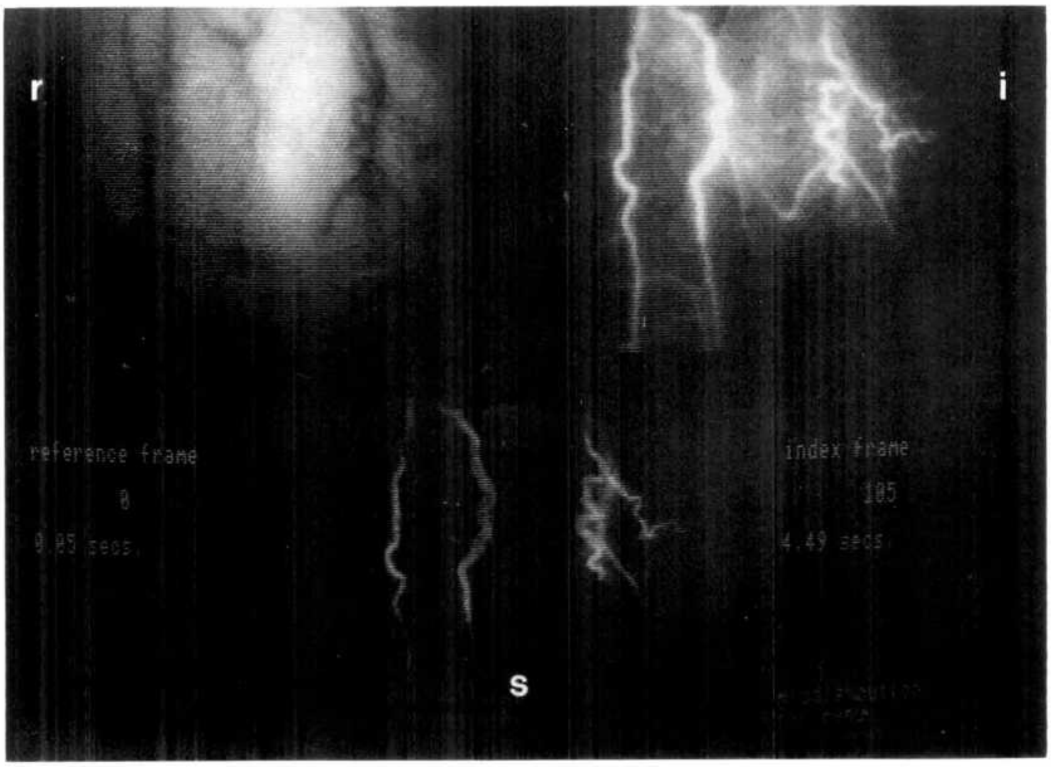

*Figure 3B*

*B: Background (auto- and pseudofluorescence) subtracted from arterial phase to enhance contrast.*

### SOFTWARE

The program is written in structured Basic and machine code. It is accessed entirely by means of the mouse, and a 'menu' remains continually on screen (Fig 2).

A video sequence is fed from a camera or videotape into the video digitiser, and the rate of transfer of frames to RAM is selected by the operator (maximum 12·5 frames/s). Up to 180 frames may be stored as 125×125 pixel images with 6 bit resolution (64 grey levels).

Images are displayed at 4 bit (16 grey level) resolution as quarter screens on a multisync monitor (NEC). This allows room to present frames from different memory locations simultaneously – usually the 'line' image in the digitiser memory and the image from the RAM location that is currently being examined (Figs 1, 2).

The video sequence (or any part of it) may be played forwards or backwards repeatedly. The transition from one frame to another is seamless.

Sequences can also be 'searched'. During this procedure the position of the mouse determines the frame that is currently displayed. By moving the mouse towards or away from him, the operator has complete control of both the moment in a sequence and the rate of display (Fig 2).

By means of a machine code subroutine two images may be subtracted in less than 0·1 second, allowing almost instant comparison (Fig 3A) or the erasure of background fluorescence (Fig 3B). Superimposition of frames is achieved by flickering between them while one is held static and the other is moved horizontally or vertically by the mouse. Alternatively, one frame (representing, for example, choroidal fluorescence or scleral autofluorescence) may be rapidly subtracted from the entire sequence. The computer memory is then updated so that the processed sequence may be replayed or searched just as were the raw data.

The program also includes facilities for measuring distances between points (or the length of a drawn line) in successive frames, which is helpful for assessing flow velocities or the spread of capillary perfusion.

Any raw or subtracted sequence may be stored on hard disc for future retrieval.

## Discussion

With the help of a powerful, fast desk top microcomputer an ophthalmologist may be given access to an entire video sequence with a directness hitherto impossible. Frames from different moments in the sequence can be rapidly compared by subtraction, and the contrast of whole sequences may be similarly enhanced.

The system has now been used for the analysis of arterial and venous blood flow direction and velocity in 20 experimental episcleral videoangiograms from normal subjects. It proved to be both more consistent and approximately 10 times faster than a previous manual method involving direct measurements from a monitor.

When a videoangiogram is displayed seamlessly at high speed, the moment of peak capillary fluorescence during first pass of the dye is clearly demonstrated. This is a time point that is independent of illumination or camera sensitivity threshold. It has been used to quantify regional filling delays within an angiographic field, particularly during the interpretation of experimental iris fluorescein videoangiograms.

Clinical angiograms from patients with scleritis and corneal neovascularisation induced by wearing a contact lens have also been successfully analysed. Although designed for fluorescein angiography, this method of image analysis is equally applicable to radiology (for example, barium swallow or cardiac catheterisation) and laboratory microscopy (for example, the observation of cultured cells). The system that is described here requires only one monitor, is very reasonably priced, and has adequate resolution for most clinical purposes. For short video sequences a recorder is not required, and time lapse video recording is also possible.

However, the presentation of all images by the computer's own display restricts the grey scale to 16 levels, and the 125×125 pixel format lowers spatial resolution. The program is therefore being adapted for use with a new video digitiser (Hawk V10; Wildvision) that is capable of capturing 256×256 pixel images at 8 bit resolution and down-loading them to RAM at 0·2 second intervals. They are displayed with 8 bit resolution on a separate monitor.

Static images are inadequate for examining dynamic events such as blood flow. Although video may result in lower spatial resolution than photography, this is offset by the greatly enhanced temporal resolution. The provision of complete control over the time base of an angiogram offers the clinician an overview of vascular perfusion that has previously been impossible and should facilitate the clinical application of videoangiography.

The evolution of this image processing system, particularly the use of a mouse to control the presentation of a video sequence, owes much to discussions with Mike Hobart.

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# Convergence excess esotropia treated surgically with fadenoperation and medial rectus muscle recessions

R Jane Leitch, John P Burke, Ian M Strachan

## Abstract

**Convergence excess esotropia has been treated with bifocals, miotics, medial rectus recession(s), fadenoperation, or a combination of these. However, comparatively few studies on the sensory status of these patients exist. We present the sensory findings in 31 children treated surgically. Twenty-one had fadenoperations combined with bimedial rectus recessions, one had a fadenoperation alone, and nine had augmented bimedial rectus recessions. Five children (16%) achieved bifoveal fusion, 22 (71%) had varying degrees of peripheral fusion, and four (13%) had no detectable binocularity after a mean postoperative follow-up of 2·4 years.**

Convergence excess esotropia is characterised by normal binocular single vision for distance (with glasses if required) but esotropia on accommodation for near fixation. Its traditional treatment has been with bifocals[1] and occasionally miotics. However, doubts have been raised about the appropriateness of long term treatment by either of these methods.[2]

The results with conventional surgery, namely unilateral or bilateral medial rectus recessions, have been mixed, while the use of the posterior fixation suture alone or in conjunction with conventional surgical techniques is accepted as an alternative. We review the sensory findings in 31 consecutive cases of convergence excess esotropia after primary surgical treatment.

## Patients and methods

Thirty-one cases of convergence excess esotropia were treated surgically over a five-year period. None had been previously treated with miotics or bifocals. Twenty-one children had bilateral medial rectus recessions combined with posterior fixation sutures placed as far posteriorly as the intraconal fat pad would allow (12–14 mm from the original insertion). 1 mm of medial rectus recession was performed for each 3 prism dioptres of distance angle measured. Two posterior fixation sutures (PFS) were placed in each medial rectus muscle (the superior and inferior sutures incorporating approximately the superior and inferior one-fourths of the muscle respectively) with 5:0 Dacron. One patient was treated with posterior fixation sutures (fadenoperation) alone. Nine cases had bilateral symmetrical augmented medial rectus recessions where 1 mm of recession was performed for each 3 prism dioptres of near angle up to a maximum of 6·5 mm of recession per eye. Our aim was to reduce the near deviation to less than 10 prism dioptres (PD) so that suppression might be reduced or eliminated and the potential for fusion facilitated. Tables 1 and 2 compare the sizes of the near angles preoperatively with the most recently measured deviations and outline the most recent sensory status of all 31 patients.

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TABLE I *Preoperative near deviation (prism dioptres), postoperative alignment, and steroacuity in 21 patients with improved binocular status after surgery*

| | *Fadenoperation plus recession group (21 cases)* | *Bilateral recession group (5 cases)* |
|---|---|---|
| Age at surgery (years) | 5·7 (range 2·5 to 9·0) | 6·8 (range 5·5 to 7·8) |
| Age at end of follow-up | 8·1 (range 5·0 to 12·0) | 9·6 (range 8·0 to 15·0) |
| Preop. near deviation (PD) | 35·6 (range 25 to >45) | 32·0 (range 25 to >45) |
| Postop. near stereoacuity (arc°) | ≤60° 4 cases | ≤60° 1 case |
| | >60°–≤140° 7 cases | >60° ≤140° 3 cases |
| | >140°–≤800° 5 cases | >140° ≤800° 1 case |
| Present near alignment of each patient | 12 E*; 1X**<br>3 microtropia | 5 E |

*E=esophoria. **X=exophoria.

## Results

Thirty-one cases of convergence excess esotropia were assessed (17 males, 14 females). Their mean age when first seen was 3·7 years (range 1·5 to 6·8 years). Their mean age at surgery was 5·7 years (range 2·5 to 9·0 years), while their mean age at most recent assessment was 8·1 years (range 5·0 years to 15·0 years). The child who had posterior fixation sutures alone had a near angle of 30 prism dioptres. Five of 22 children who had posterior fixation sutures required further surgery, with resultant satisfactory realignment. Two had been initially overcorrected, while three were initially undercorrected.

There was a significant overall reduction in the size of the near deviation postoperatively, most cases being phoric or with a residual small angle manifest squint (Table I). In many cases a microtropia was noted for near with the 4-dioptre prism test. There was a significant improvement in binocularity and in stereoacuity postoperatively in 21 children (68%) (Table I). In eight cases (26%) (Table II) cosmesis was improved without a noticeable improvement in binocularity. Binocularity was lost in two children, though cosmesis was satisfactory. There were no cases of convergence weakness and no intraocular complications postoperatively. Lateral incomitance, while common, was not marked or symptomatic in any of our patients following fadenoperation.

## Discussion

Despite having binocular single vision for distance fixation, children with convergence excess esotropia are not infrequently difficult to treat and results are often disappointing. Miotics were reported to be ineffective.[2] Moreover, they have numerous side effects, some of which may

TABLE II *Preoperative near deviation (prism dioptres) and postoperative alignment in 10 patients, with little change (8 cases) or apparent deterioration (2 cases) in postoperative binocular status*

| | *Fadenoperation plus recession group (5 cases)* | *Bilateral recession group (4 cases)* | *Fadenoperation (1 case)* |
|---|---|---|---|
| Age at surgery (years) | 5·1 (range 4·5 to 6·5) | 5·8 (range 3·1 to 9·0) | 4·0 |
| Age at end of follow-up | 7·2 (range 6·0 to 9·1) | 8·1 (range 3·1 to 9·8) | 6·0 |
| Preop. near deviation (PD) | 40 (range 30 to 45) | 31 (range 20 to 40) | 30 |
| Postop. near stereoacuity (arc°) | 2 small PFR[*]<br>3 no BSV[†] | 2 small PFR<br>200°, 400° | Small PFR |
| Present near alignment | 3 E[‡], 2 ET[§] | 1 E, 1 X,[‖] 2 ET | 1 E |

[*]PFR=Prism fusion range. [†]BSV=binocular single vision. [‡]E=esophoria. [§]ET=esotropia. [‖]X=exophoria.

be severe.[3] The traditional treatment, more especially in the United States of America, has been with bifocals,[1,4] but little information is available on the sensory findings in such patients and the efficacy of this therapy in comparison with other methods.[2,4,5] Indeed, correct fitting of bifocal and compliance with their wear is often less satisfactory in active children than in adults.

Von Noorden *et al* evaluated bifocals in 84 children.[4] Twelve (14%) patients were able to fuse without bifocals at the end of therapy; in 19 (22%) the bifocal power could be reduced. Thirty-nine (46%) remained dependent on bifocals, and in 14 (17%) fusion had deteriorated in spite of therapy. Tillson and Pratt-Johnson[2] suggested that bifocals were ineffective even in compliant patients in preventing the eye from turning in at all near distances. In their series of 120 children surgery (bimedial rectus recessions) was performed only if children had a distance esotropia greater than 10 prism dioptres. They noted that the sensory results in those prescribed bifocals were comparable with those treated surgically. Only 9% of those treated with biofocals or surgery achieved bifoveal binocular single vision for near (<60° arc) and distance, while 76% achieved peripheral fusion. The children in our study differed in that none had a documented distance esotropia, and a different surgical procedure was employed. Only five cases (16%) achieved bifoveal binocular single vision for near and distance (four of 21 cases of posterior fixation sutures with medial rectus muscle recessions; one of nine cases of bilateral medial rectus muscle recessions), while 22 (71%) cases achieved variable stereopsis. In two cases (6%) binocular potential was lost despite cosmetically satisfactory alignment.

Conventional muscle surgery techniques have been used to treat convergence excess esotropia with mixed success.[6-8] Kushner *et al*,[9] believing that conventional recessions were associated with frequent undercorrections, conducted a prospective study of 46 patients with partially accommodative esotropia with a high AC/A ratio. One group had bilateral medial rectus recessions with posterior fixation sutures, while the other group had augmented bilateral medial rectus recessions. Their data suggested that better postoperative alignment was achieved by the latter procedure. Reynolds and Hiles[10] used a variety of procedures in conjunction with the posterior fixation suture. Most of their bifocal wearers could discard their glasses, but further details on sensory findings were not published.

There are a number of conflicting reports on the variability in the postoperative deviation following either posterior fixation suture alone or in combination with medial rectus muscle recessions.[11-13] Kushner *et al*[9] noted that three of 21 patients with combined bilateral medial rectus muscle recessions and posterior fixation sutures were overcorrected, while some were significantly undercorrected. In our series five of 21 cases required reoperation, with satisfactory realignment. None of our patients suffered vision threatening intraocular complications after a mean postoperative follow-up of 2·4 years. Lyons *et al*[14] have recently retrospectively reviewed 100 fadenoperations and affirmed the relative safety of the procedure.

The traditional treatment of convergence excess esotropia (high AC/A ratio) in children has been with biofocals. We used the posterior fixation suture, bilateral medial rectus recessions, or a combination of these as a primary therapy. The results of postoperative alignment and steroacuity compare favourably with those previously published. We believe that the posteror fixation suture is an effective primary treatment of convergence excess esotropia when compared with the known advantages and disadvantages of existing therapeutic methods.[14,15]

The authors thank Jane Parkinson and the staff of the orthoptic department for their help with this study.

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*British Journal of Ophthalmology*, 1990, 74, 280–282

# Quantitative analysis of collagen content and amino acids in trabecular meshwork*

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## Abstract

**The purpose of this study was to compare collagen content in the TM of normal and glaucomatous eyes, and to establish whether collagen levels change with age. Collagen content was measured in 30 normal and 27 age matched glaucoma trabeculectomy specimens by the sirius red dye binding technique, and in 14 normal and 15 age matched glaucoma specimens by amino acid analysis. Both dye binding data and amino acid analysis showed no statistical difference between normal and glaucoma samples. Age had no significant effect on mean optical densities or on the collagen-specific amino acids proline, hydroxyproline, and hydroxylysine. Amino acid variability, however, was statistically different between the two groups. These results indicate that mean collagen levels in the trabecular meshwork of glaucomatous eyes do not differ from those in normal eyes.**

The cause of decreased outflow facility in primary open-angle glaucoma (POAG) remains controversial. However, abnormal trabecular meshwork (TM) collagen levels have been implicated by some authors.[1] Changes in hydroxyproline concentration have been reported in the serum and urine of glaucoma patients.[2] In comparison with normal samples increased levels of type I collagen have been reported in glaucomatous samples of human TM.[3] An overall decrease in collagen types I, III, IV, and V has also been reported in glaucomatous eyes.[4] However, other workers have reported no difference in collagen-specific amino acids in the TM of glaucomatous and control eyes.[5] A marked increase of lattice ('curly') collagen and elastic material has been reported in the TM of eyes of older people.[6] Age related increases in type I and IV collagen have also been reported in normal TM.[7] The purpose of this study was two-fold: (1) to compare collagen levels in glaucomatous and normal TM, and (2) to determine whether age related changes occur in either group.

## Materials and methods

Thirty normal and 27 age matched glaucoma trabeculectomy specimens from patients ranging in age from 39 to 90 years were obtained from fresh donor eyes and surgical trabeculectomies. All donor eyes and TM specimens were fixed in 10% buffered formalin (Fischer Scientific Co, Fairlawn, NJ, USA) within 12 hours of enucleation. Trabeculectomy specimens were excised under a surgical microscope by Watson's method of trabeculectomy.[8] Each block of tissue was 2×2 mm which contained TM plus a small amount of sclera and cornea.

### DYE BINDING STUDY

Tissue sections were processed and embedded in paraffin. Each tissue sample was analysed separately three times, with 20 10 μm sections being used per trial. Dry tissue weights were measured on an electrical balance (Mettler AJ100) prior to staining. The sections were placed on glass slides, deparaffinised, and hydrated in xylene, 100%, 80%, and 50% ethanol and distilled water, each for intervals of 4 minutes. Tissue sections were immersed in Coplin jars containing 0·1% sirius red dye (Chroma-Gesellschaft, Stuttgart, Germany) in saturated picric acid (BDH Chemicals, Toronto, Canada). The sections were incubated at room temperature and shaken for 30 minutes. Unbound dye was discarded by repeated rinsings of saturated picric acid and distilled water. The bound dye was eluted from the tissue by scraping the sections into a solution of 0·1 N NaOH in absolute methanol (1:1, v:v), and allowing it to stand for 30 minutes at room temperature. After centrifugation at 4000 rpm the supernatant was removed and optical densities (OD) were measured on a spectrophotometer (Gilford 2400) at 540 nm. This technique was modified from that used by Yue *et al.*[9]

### AMINO ACID ANALYSIS

Fourteen normal and 15 age matched glaucoma TM specimens were obtained by the methods outlined above. Each tissue sample consisting of 20 10 μm sections was deparaffinised and hydrated, and then scraped into separate test tubes. The samples were then freeze dried in a lypholyser at 48 atm (4850 kN/m$^2$) and −50°C, and dry weights were determined. Samples were hydrolysed with 6 N HCl in vacuo at 106°C for 24 hours, and then dried and redissolved with 300 μl of doubly distilled water. Collagen specific amino acids (proline, hydroxyproline, and hydroxylysine) were measured in nmol/mg of dried tissue on an amino acid analyser (Beckman 121M).

Dye binding data were analysed by an F test to compare mean optical densities between groups that were controlled for age. Group differences in mean amino acid concentrations were also measured with the same test statistic. The effects of age on optical densities and amino acid levels for both groups were also analysed by an F test.

## Results

Results from the dye binding study showed mean optical densities of 0·525 (SEM 0·036) and 0·413 (SEM 0·045) for normal and glaucoma groups respectively (Fig 1). There was no statistical difference in mean optical density

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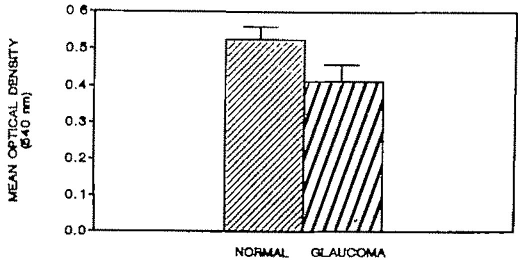

*Figure 1: Dye binding data illustrating mean optical densities (with SEM) for normal and glaucoma TM samples.*

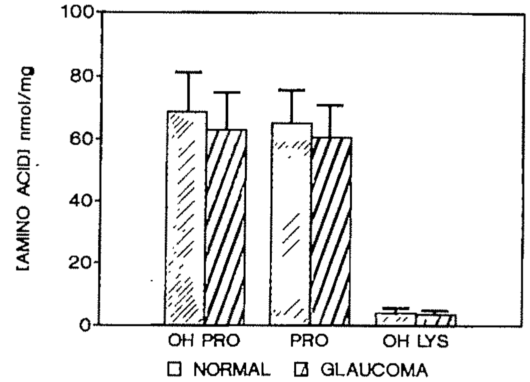

*Figure 3: Mean concentration (nmol/mg) (with SEM) of hydroxyproline (OH PRO), proline (PRO), and hydroxylysine (OH LYS) for normal and glaucoma TM samples. Four values were treated as missing.*

between these groups. The change in optical density in the glaucoma group showed a slight increase with age, whereas the optical densities of normal eyes were virtually constant with increasing age (Fig 2). The difference between both groups, however, was not statistically significant.

Mean concentrations for all three amino acids were slightly lower for the glaucoma group, but the differences were not statistically significant. The mean hydroxyproline concentration for normals was 68·68 (SEM 12·56) nmol/mg as compared to 63·03 (SEM 11·76) nmol/mg for glaucoma samples. The mean proline concentration was slightly lower for normal and glaucoma groups at 65·16 (SEM 10·33) nmol/mg and 60·74 (SEM 10·28) nmol/mg respectively. The mean concentration for hydroxylysine was 4·15 (SEM 0·77) nmol/mg for normal samples as compared with 3·61 (SEM 0·64) nmol/mg for glaucoma samples (Fig 3). Amino acid concentrations appeared to decrease slightly with increasing age for both normal and glaucoma groups. However, the differences in amino acid concentration as a function of age were not statistically significant. Hydroxyproline is shown as a representative example (Fig 4).

Comparison of variations of amino acid concentration revealed more variable hydroxyproline, proline, and hydroxylysine concentrations in the glaucoma group than in the normal persons as a function of age. The probabilities of the statistical differences in variability between the two groups were: hydroxyproline ($p=0·001$), proline ($p=0·002$), and hydroxylysine ($p=0·0001$).

## Discussion

Ten genetically distinct types of collagen have been described in mammalian tissues.[10] Type I collagen constitutes the major collagen fraction in the cornea and sclera, while type III is generally found to coexist with type I.[2] Immunohistochemical studies and amino acid analyses have detected types I, III, and IV in the trabecular meshwork and lamina cribrosa.[11-13]

Histochemical methods have been used by others to estimate collagen concentrations in ocular tissue sections prepared from formalin-fixed, paraffin-embedded samples.[9] Sirius red dye is known to bind collagens preferentially to other proteins, specifically types I, II, and III.[14] This dye binding method provides a quantitative measurement of collagen content where the bound dye is proportional to the total amount of collagen present. Our results showed no statistical difference between mean optical densities of normal and glaucoma eyes, suggesting no difference in the amounts of collagen types I and III. These results differ from the report of Millard *et al* of increased levels of type I collagen in glaucomatous TM.[3] They evaluated collagen levels using silver staining techniques and sodium dodecyl sulphate polyacrylamide electrophoresis. However, since we did not selectively test for type I collagen, there is a possibility that other collagen types may have masked the total quantitation of type I collagen.

Although we found no differences in amounts of collagen types I, III, and IV in the trabecular meshwork of normal and glaucoma eyes, Conner *et al* have recently reported at least a 50% decrease of collagen types III and IV in glaucomatous eyes and a 46% decrease of type I in glaucomatous eyes.[4] One possible explanation for our results includes the fact that we used trabecular meshwork samples derived from trabeculectomy specimens. Such samples have two drawbacks: firstly, they are always contami-

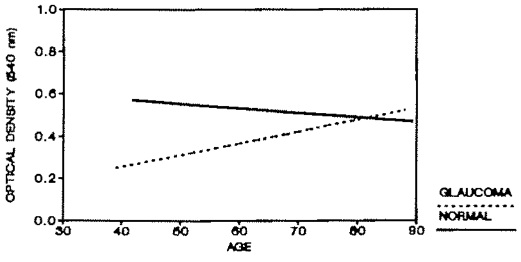

*Figure 2: Effect of age on optical densities for normal and glaucoma TM samples.*

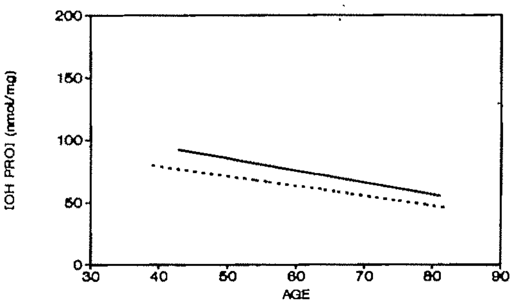

*Figure 4: Representative illustration of the effect of age on amino acid concentration (nmol/mg). The concentrations for hydroxyproline (OH PRO) as a function of age are shown. Four values were treated as missing. Glaucoma ........ Normal ——*

nated by small amounts of cornea and sclera; and, secondly, the possibility exists that changes that occur in glaucoma, if any, could be masked by the small sample size of TM from the specimens. However, as trabecular meshwork specimens were the only source of glaucoma specimens for this study, such drawbacks were unavoidable.

Amino acid analysis is a well recognised method of determining tissue collagen concentrations.[5,7,13] The results of our amino acid analyses indicated no difference in mean concentrations of proline, hydroxyproline, and hydroxylysine in normal and glaucoma eyes, confirming the dye binding data.

Results from both parts of this study indicated that age related effects on collagen concentrations do not exist in either normal or glaucoma eyes in relation to the specific collagen types and amino acids that were tested. Although we found no differences in mean amino acid concentrations in both groups, significant differences were found in the variances of both groups, especially with hydroxylysine.

The significance of this finding is not known. A larger study on amino acid levels from normal and glaucoma trabecular meshwork may clarify this finding. For all three amino acids measured, normal samples showed greater variability than glaucoma samples. Using amino acid analysis, Horstmann *et al*[7] reported a rough estimate of the distribution of collagen types in TM based on 3-hydroxyproline/4-hydroxyproline ratios. These authors found age related increases in collagen types I (55% to 70%) and IV (2% to 5%). These age related increases were slight but not statistically significant. In this respect the two studies are similar.

In conclusion, collagen concentrations as measured by dye binding and amino acid analysis showed no difference between normal and glaucomatous eyes. Amino acid levels in normal samples, however, were much more variable than glaucoma samples. Age had no effect on collagen levels in either group. Abnormally high or low trabecular meshwork collagen levels in glaucomatous eyes therefore do not appear to be the cause of decreased outflow facility in primary open-angle glaucoma.

Donated eyes and specimens from surgical trabeculectomies were kindly provided by the Eye Bank of Canada (Ontario Division), Oregon Lions Eye Bank, and the Ophthalmic Pathology Laboratory (Toronto, Canada), respectively. Statistical analysis was supervised by Professor M Chipman, Clinical Research Support Unit, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Canada.

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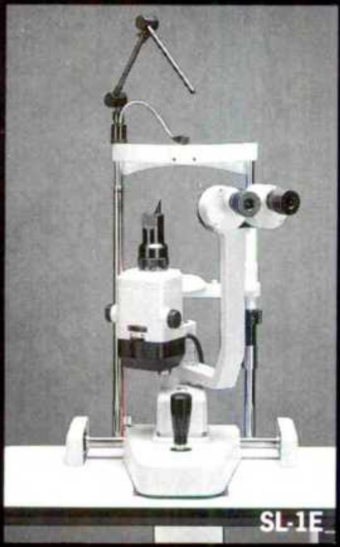

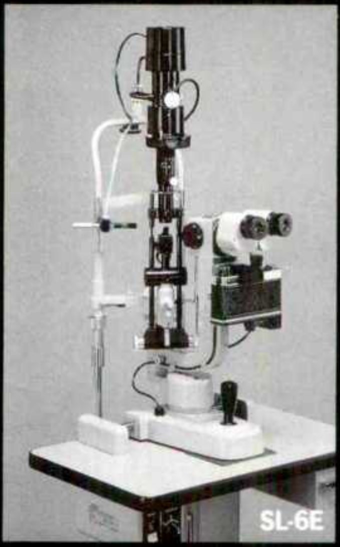

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# A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis

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## Abstract

**Forty-three patients with active herpetic disciform keratitis were entered into an open study to compare the efficacy of oral acyclovir (400 mg) with acyclovir ophthalmic ointment (3%) to inhibit viral replication during treatment with 0·05% prednisolone eye drops. All patients, regardless of the mode of therapy, were treated five times a day until they were healed. The mean time to heal in the oral group was 25·9 days and in the topical group was 25·3 days. Resolution of lacrimation was significantly faster in the oral group (12·1 days versus 27·6 days). The patients on tablets also showed a greater improvement in visual acuity. No statistically significant differences were found between the two groups in the incidence of recurrences over a three-year post-treatment period. It is concluded that oral acyclovir treatment is an effective alternative to ophthalmic ointment in the management of herpetic disciform keratitis.**

The pathogenesis of herpetic disciform keratitis is not fully understood, but the disease may be the result of a delayed hypersensitivity reaction to viral replication in the corneal stroma. In moderate and severe disease the use of local steroids with an antiviral therapy is justified.[1] The use of steroids alone can result in a high complication rate of dendritic ulceration,[2] and the use of an antiviral agent alone has been shown to be inadequate.[1]

Acyclovir is a potent and selective inhibitor of herpes simplex virus replication. When administered topically it is well tolerated and effective for the treatment of dendritic keratitis.[3] It has also been used successfully for the treatment of disciform keratitis when combined with betamethasone.[1] Therapeutic concentrations within the eye can be attained by local[4] or systemic administration.[5-7] This study compares local and systemic treatment with acyclovir in a group of patients suffering from active herpetic disciform keratitis to ascertain firstly whether the route of application favourably affects the outcome of active disease, and secondly whether there is any significant difference in subsequent recurrence rates. All patients received local dilute steroids.

## Methods and materials

Patients aged 18 years and over with a clinical diagnosis of either primary or recurrent disciform keratitis were entered into this open, randomised comparative study over a period of three years. The diagnosis was based on clinical appearance and history. Patients were excluded if they had been treated with specific antiviral therapy within the previous 14 days or with topical or systemic steroids within the previous 30 days. Patients with active epithelial disease, renal function impairment, or of child bearing potential were also excluded. Informed consent was obtained.

All patients applied prednisolone (0·05%) eye drops[*] five times daily to the affected eye. In addition the patients were randomly allocated to one of two treatment groups. One group received acyclovir ointment (3%) and the other group received acyclovir tablets (400 mg). Both medications were administered at four-hourly intervals, but patients omitted the dose in the middle of the night. They were treated until healing was evident. When the keratitis had resolved, acyclovir treatment was terminated and the steroid dosage was gradually tapered over a one-month period. Mydriatics and glaucoma therapy were given as necessary.

The patients were followed up as often as clinically necessary but at least weekly during treatment and then at 1, 3, 6, and 12 months. Patients were then seen at yearly intervals when possible.

On entry and on subsequent visits the severity of pain, photophobia, lacrimation, and grittiness sensation was assessed on a 0–3 score, where 0=none, 1=mild, 2=moderate, 3=severe. A full ocular examination was also carried out with a slit-lamp biomicroscope. Assessments included the severity of conjunctivitis (redness, scarring, follicles), extent of stromal oedema and infiltration, disturbances in Descemet's membrane, presence and extent of uveitis, and presence of endothelial cells and keratic precipitates. The visual acuity of the affected eye (uncorrected and with pinhole) was assessed by means of the Snellen chart. Intraocular pressure was measured by a tonometer.

Any signs or symptoms potentially attributable to acyclovir administration were recorded.

TABLE I *Patient demography*

| | *Tablet recipients* | *Ointment recipients* |
|---|---|---|
| No. of evaluable patients | 20 | 19 |
| No. of females | 10 | 7 |
| No. of males | 10 | 12 |
| Mean age (SD) in years | 56·3 (17·86) | 49·7 (19·49) |
| % Patients with previous disciform keratitis | 50 | 63·2 |
| % Patients with previous cutaneous herpes | 63·2 | 47·1 |
| % Patients received previous antiviral therapy | 83·3 | 80·0 |
| % Patients received previous steroid therapy | 75·0 | 71·4 |
| No. of patients using concomitant medication | 15 | 16 |
| No. of patients receiving antiglaucoma therapy | 6 | 4 |

SD=standard deviation.

Patients were withdrawn from the trial if there were signs of increased inflammatory activity or if their condition remained static for 14 days.

The main criteria used to assess healing were the absence of stromal oedema, ciliary injection, and keratic precipitates. The times to resolution of individual signs and symptoms and also of healing were analysed by the Mantel-Cox test as applied by the BMDP statistical package. Unaided Snellen visual acuity was used in the analysis except in patients who had been given mydriatics, when a pinhole was used. Visual acuity scores on entry, changes in visual acuity from entry, and changes in intraocular pressure from entry between the two groups were compared by Student's *t* test. Recurrence rates were analysed by the Pearson $\chi^2$ test. p Values of $\leq$0·05 were considered statistically significant.

## Results

### PATIENT DEMOGRAPHY

Forty three patients entered the study. Two patients failed retrospectively to meet the entry criteria and two defaulted during the study. The remaining 39 patients were entered. Of these patients 19 received acyclovir ophthalmic ointment and 20 received acyclovir tablets. Table I shows the patient demography for each treatment group.

### RESOLUTION OF SYMPTOMS AND SIGNS

The rates of resolution of the clinical symptoms of pain, photophobia, and grittiness were not significantly different between the two treatment groups. However, resolution of lacrimation was significantly faster in the oral group, with a mean of 12·1 days for the tablet recipients and 27·6 days for the ointment recipients (p=0·02).

The mean times to resolution of conjunctivitis (redness, scarring, and follicles), stromal infiltration, stromal oedema, disturbances in Descemet's membrane, and uveitis were not statistically different between tablet recipients and the ointment recipients (p>0·15, Table II).

Complete healing was observed in patients on tablets in a mean time of 25·9 days and in the ointment group in a mean time of 25·3 days. This difference was not statistically significant (p>0·05, Fig 1). An average decrease in intraocular pressure of 4·6 mmHg was noted among patients receiving oral acyclovir, and an average decrease of 4·1 mmHg was noted among patients receiving ophthalmic ointment. This difference was also not statistically significant.

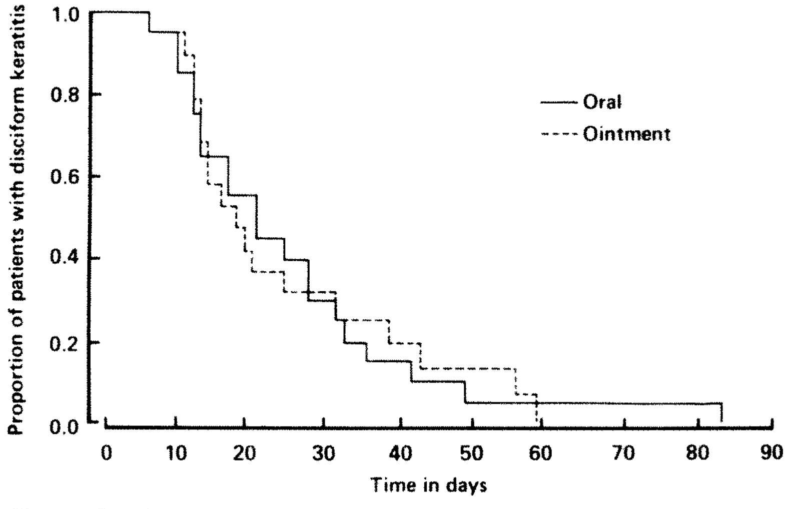

*Figure 1: Cumulative frequency distribution of time taken to complete healing.*

TABLE II *Resolution times for clinical signs*

| | *Mean resolution time (days)* | | |
|---|---|---|---|
| | *Ointment* | *Tablet* | *p Value* |
| Conjunctivitis (redness) | 14·3 | 17·2 | 0·56 |
| Conjunctivitis (scarring) | 11·0 | 4·0 | 0·16 |
| Conjunctivitis (follicles) | 11·0 | 3·0 | 0·06 |
| Stromal oedema | 26·2 | 24·3 | 0·8 |
| Stromal infiltration | 92·8 | 44·8 | 0·8 |
| Folds in Descemet's membrane | 7·4 | 8·8 | 0·79 |
| Uveitis (cells) | 9·1 | 8·6 | 0·94 |
| Uveitis (flare) | 6·0 | 6·5 | 0·6 |
| Endothelial cells | 16·8 | 12·2 | 0·29 |
| Endothelial keratic precipitates | 73·3 | 30·4 | 0·42 |

The median visual acuity scores on entry for the two treatment groups were comparable (p>0·05), and were 6/24 (0·25) for the tablet recipients and 6/36 (0·17) for the ointment recipients. The mean change in visual acuity from entry was 0·13 in the ointment group, and 0·28 in the tablet group (p=0·02). Thus there was a significantly greater improvement in vision between entry and the end of treatment in the tablet group.

Both acyclovir ointment and tablets were well tolerated. Two patients receiving acyclovir ointment had punctate epithelial keratopathy which persisted throughout the treatment period but cleared immediately on stopping the medication. No adverse reactions were reported by patients receiving acyclovir tablets.

### RECURRENCES DURING THE FOLLOW UP

Table III summarises the recurrences of disciform keratitis for each treatment group. Attempts were made to follow up the patients for a maximum of three years. One patient died during the first year of follow-up, one in the second year, and three in the third year. None of these deaths was associated with recurrences or with acyclovir treatment. No significant difference was found between the recurrence rates in the two treatment groups.

Two patients in the ointment group underwent penetrating keratoplasty, one in the first year and one in the second year. Both progressed well and have not suffered any postoperative recurrence.

In the ointment group one patient developed a dendritic ulcer six months after healing. In the oral group three patients each developed one dendritic ulcer at three months, six months, and 12 months. No patient developed a dendritic ulcer during the period of treatment, and in particular none occurred during the month of unprotected reducing-dose steroid therapy. Trophic ulcers occurred in both treatment groups, but there was no difference in frequency between the two groups.

## Discussion

No statistically significant differences were

TABLE III *Incidence of recurrent attacks of disciform keratitis in each year of follow-up*

| | *1st Year No. of patients* | | *2nd Year No. of patients* | | *3rd Year No. of patients* | |
|---|---|---|---|---|---|---|
| *No. of recurrences* | *Tablet* | *Ointment* | *Tablet* | *Ointment* | *Tablet* | *Ointment* |
| 0 | 9 (50%) | 11 (61·6%) | 6 (33·3%) | 7 (43·8%) | 4 (66·7%) | 5 (41·7%) |
| 1 | 7 | 6 | 6 | 8 | 1 | 4 |
| 2 | 2 (50%) | 1 (38·4%) | 5 (66·7%) | 0 (56·2%) | 1 (33·3%) | 3 (58·3%) |
| 3 | 0 | 0 | 1 | 1 | 0 | 0 |
| Total followed up | 18 | 18 | 18 | 16 | 6 | 12 |
| | p=0·74 | | p=0·15 | | p=0·60 | |

found between the tablet recipients and ointment recipients in the rates of resolution of pain, grittiness, and photophobia. The duration of lacrimation was significantly longer from patients receiving ointment, which might well be related to the application of a paraffin film to the eye. The mean time to resolution of clinical symptoms in the ointment group ranged from 10 to 28 days. This is longer than previously reported in a study where all patients with deep stromal keratitis treated with acylovir ointment and 2·5% prednisolone showed resolution of symptoms in one week.[9] However, in the latter study patients were entered if they showed signs of stromal infiltration and were excluded if they had oedema of the disciform type. In addition the concentration of prednisolone used was 50 times greater than that used in the present study.

The median visual acuity score on entry was 6/36 in the ointment group and 6/24 in the oral group. Although visual acuity in each group on entry was comparable, tablet recipients showed a significantly greater improvement in visual acuity. The application of a film of paraffin to the eye is likely to have a temporarily detrimental effect on visual acuity; further, in patients whose vision is already impaired because of the disease process, this effect may be more pronounced. In such instances, the oral formulation may be preferred.

The mean time to healing in the present study was 25·3 days for the ointment recipients. This is similar to the results reported by Collum and Grant.[10] They reported that when patients with disciform keratitis were treated with acyclovir ointment and 0·01% betamethasone the mean time to complete healing was 21 days. No significant difference in the mean time to healing was found between oral and topical therapy in the present study.

Topical or systemic acyclovir administration of acyclovir appears to be associated with comparable recurrence rates. This evidence supports the current concept that the antiviral agents available do not eradicate herpes virus, be it latent in the central nervous system or sustained by chronic infection such as dacryoadenitis.[11]

Both acyclovir tablets and acyclovir ointment were well tolerated. Only two patients in the ointment group experienced diffuse superficial punctate keratopathy, while no adverse events were reported by the tablet recipients. No patient developed dendritic ulceration as a complication during treatment. This is consistent with the good safety profile of acyclovir in various formulations established over the past years.

The results of this study have shown that oral acyclovir (400 mg) taken five times a day is as efficacious as acyclovir (3%) ophthalmic ointment administered five times a day in inhibiting viral replication during the treatment of disciform keratitis with prednisolone (0·05%). It is evident that, while local administration of acyclovir is the usual route, systemic acyclovir is an equally effective alternative and may be preferred in certain situations such as the uncooperative child or in an arthritic patient, who may find difficulty in the administration of the ointment. For patients who require topical eye preparations for the treatment of concurrent ocular complications other than herpetic eye diseases the use of oral acyclovir may simplify the treatment regimen, and reduce the potential for local drug or formulation interactions.

The authors are indebted to Ms M Small and Mr D Jones at the Wellcome Research Laboratories for their support and statistical analysis of this study.

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# Ocular herpes simplex virus infections: reduced sensitivity to acyclovir in primary disease

S J Charles, J J Gray

**Abstract**

**Forty isolates of herpes simplex virus (HSV) obtained from ocular herpetic infections were assayed for their sensitivity to five antiviral agents. There were wide ranges of sensitivity to foscarnet, idoxuridine, and vidarabine, but the majority were sensitive to acyclovir and ganciclovir. Reduced sensitivity to acyclovir was seen in four isolates, all of which were from primary infections acquired in the community and without a previous history of treatment with antiviral drugs.**

With the widespread use of antiviral drugs in herpetic infections the development of resistant herpes simplex virus (HSV) strains must be monitored. In-vitro virus resistance to acyclovir (ACV) may be selected for by passage in cell culture in the presence of the drug.[1 2] Resistant strains arise from alterations at one or both of the gene loci coding for virus-specific enzymes thymidine kinase (TK) and DNA polymerase (DNA-pol) and may emerge during treatment with ACV.[3]

In a recent study of all HSV isolates in this hospital[4] it was noted that isolates obtained from ocular infections had a reduced sensitivity to ACV compared with infections at other sites.

The present study aimed to evaluate the sensitivity of HSV isolates to a range of antiviral drugs, including ACV, in the entire population of patients presenting to the Ophthalmology Clinic with herpetic eye disease, together with isolates from ocular infections sent to the virology laboratory from general practitioners. The active concentrations of antiviral drugs at the site of ocular infections are not well known, and so antiviral resistance should be considered relative to sensitive strains. It seems reasonable to consider that isolates showing a greater than 10-fold increase in the inhibitory concentration of the drug above the mean value for sensitive isolates may be significant in terms of reduced effectiveness of therapy.[5]

## Materials and methods

### PATIENTS

A total of 40 isolates of HSV were obtained from 35 patients with ocular infections. These included 30 consecutive patients seen with herpetic eye disease in the Ophthalmology Clinic over a 12-month period from July 1988 and isolates sent from general practitioner clinics over the same period (five patients). Virus was isolated from two patients during consecutive episodes of infection and from more than one site in three patients during the same episode.

### VIRUS ISOLATION

Swabs were collected in virus transport medium (2 ml Hanks's buffered saline with 1% bovine albumin) from lesions of patients with suspected HSV infection of the eye. A volume of 100 μl was inoculated into cultures of human amnion, HEp2, and MRC-5 cells, which were then rolled for 21 days at 37°C. Cultures showing a cytopathic effect characteristic of HSV were stored at −20°C. Serotyping of the HSV isolates was performed by direct immunofluorescence (Boots-Celltech Diagnostics Ltd.).

### CONTROLS

Isolates of HSV designated DM 21 (a TK-deletion mutant), TP 2·5 (a DNA-pol mutant), and R9C2 (a TK and DNA-pol mutant), all resistant to ACV, were grown in cultures of human amnion cells for use as controls, as was a strain, sensitive to ACV, designated SC16.

### ANTIVIRAL AGENTS

Five agents all reported to be active against HSV were used: acyclovir,[6] ganciclovir,[7] foscarnet,[8] idoxuridine,[9] and vidarabine.[10]

### DYE UPTAKE TEST

Virus growing in cultures of cells reduces the uptake of the vital stain neutral red by the cells. When the assay is performed in microtitre plates, the dye can be eluted and its concentration measured colorimetrically.[11] Isolates of virus were screened for susceptibility to concentrations of each antiviral agent from 0·05 μg/ml to 100 μg/ml. They were thawed and diluted 1 in 10 and 1 in 100 in a suspension of vero cells (100 000 cells/ml) in growth medium (BSS 199, 5% FBS). 100 μl of each dilution was placed in alternate rows on the microtitre plate and an equal volume of antiviral drug, at varying concentrations, was then added to each well. Cell controls and virus controls were included with each isolate, and the plates were incubated at 37°C in an atmosphere of 5% carbon dioxide for three days.

After incubation the medium was aspirated from the wells and replaced with 50 μl of the vital stain neutral red (0·15% in phosphate buffered saline (PBS) at pH 6·5). The plates were then incubated for one hour at 37°C, after which the stain was removed by aspiration and the wells washed twice with PBS pH 6·5. The dye was rendered soluble by addition of 100 μl phosphate ethanol buffer (PBS pH 4·5 containing 10% ethanol). The optical density was read at 510 nm. End points were taken as the lowest concentration of antiviral agent to inhibit growth of the virus by 50% ($IC_{50}$) when compared with

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TABLE I *Principal presenting signs of patients with ocular infections from whom HSV was isolated*

| *Principal ocular sign* | *Number (n=35)* |
|---|---|
| Dendritic ulcer | 13 |
| Other corneal epithelial disease | 5 |
| Perforated corneal ulcer | 1 |
| Conjunctivitis | 8 |
| Blepharitis | 8 |

control wells containing virus dilutions and cells only.

## Results

### CLINICAL SPECTRUM

The spectrum of herpetic eye disease seen is shown in Table I. The most common presenting sign was dendritic ulceration, seen in 37% cases.

All isolates were HSV type 1. Twenty-one cases were suffering from a first clinical herpetic infection, nine cases were recurrent herpetic eye disease, and five had a past history of herpes labialis. Only five patients had previously been treated with ACV.

### VIRAL SENSITIVITIES

*Idoxuridine.* There was a wide distribution of IC$_{50}$ from <0·05 μg/ml to 100 μg/ml, mean 28·35 μg/ml (Fig 1).

*Vidarabine.* IC$_{50}$ ranged from <0·50 μg/ml to 100 μg/ml, mean 18·36 μg/ml.

*Foscarnet.* IC$_{50}$ ranged from <0·50 μg/ml to 100 μg/ml, mean 21·57 μg/ml.

*Acyclovir.* The majority of isolates (35 out of 40) were sensitive to ACV (<0·05 μg/ml), though three had significantly reduced sensitivity and one, with an IC$_{50}$ of 10 μg/ml, was resistant to ACV (Fig 2). The clinical background of these four isolates will be discussed. The mean IC$_{50}$ was 0·33 μg/ml, but after excluding the isolate with IC$_{50}$ of 10·00 μg/ml this was 0·08 μg/ml.

*Ganciclovir.* The majority of isolates were sensitive (IC$_{50}$ <0·05 μg/ml), though the isolate found to be resistant to ACV was also resistant (IC$_{50}$ 10·00 μg/ml). The mean IC$_{50}$ to ganciclovir was 0·32 μg/ml (0·025 μg/ml after excluding the isolates with IC$_{50}$ 10·00 μg/ml).

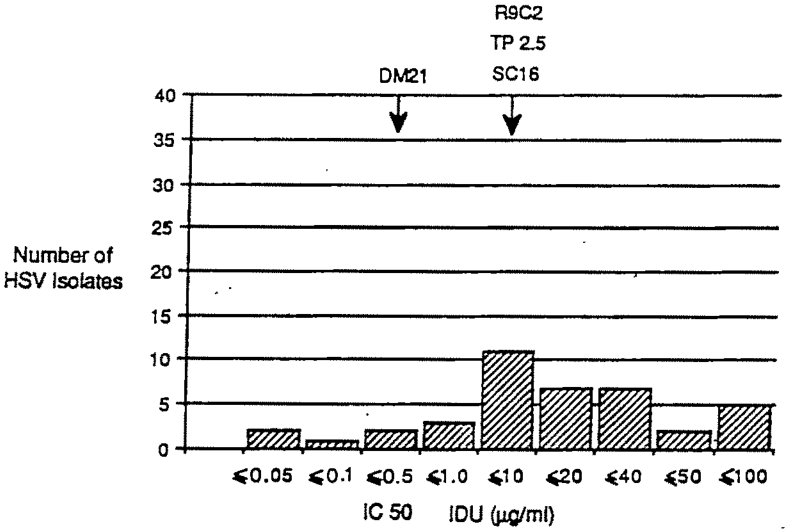

*Figure 1: Distribution of idoxuridine (IDU) IC$_{50}$ values in HSV isolates in patients with ocular infection. IC$_{50}$ values for control strains (see text) are also shown.*

## Discussion

This study, using a dye uptake assay, has shown that the majority of HSV isolates from patients with herpetic eye disease are particularly sensitive in vitro to ACV. A total of 87·5% of isolates were sensitive to ACV with IC$_{50}$ of less than 0·05 μg/ml. Isolates were also sensitive to ganciclovir in a similar distribution, as would be expected from its similar mode of action,[6] but there was a wider distribution of sensitivities to the other antiviral agents. A total of three out of 40 (7·5%) isolates had reduced sensitivity to ACV and one out of 40 (2·5%) was resistant.

It might be expected that resistant isolates would be seen in patients with a previous history of treatment with ACV. However, the isolate with an IC$_{50}$ of 10·00 μg/ml ACV was obtained from a 12-year-old asthmatic boy suffering from a primary attack of HSV blepharitis at the time of a hospital admission with pneumonia. No causative organism for the pneumonia was isolated, and he responded to intravenous antibiotics. He was not known to have been in contact with active HSV infection, though his father had had herpes labialis many years previously (and had never received ACV). This may indicate that resistant strains of HSV exist in the general population, though we cannot exclude the possibility that a resistant strain was selected during virus isolation. This resistant strain was sensitive to IDU, foscarnet, and vidarabine.

Of the three isolates with significantly reduced ACV sensitivities (IC$_{50}$ 0·5 μg/ml) none had any history of recurrent HSV infection or previous treatment with ACV. One was a case of follicular conjunctivitis associated with a first attack of herpes labialis and the other two were first dendritic ulcers. All resolved on treatment but one recurred. The isolate recovered from the recurrent infection was sensitive to ACV (IC$_{50}$ <0·05 μg/ml). The sensitive strain may have established the latent infection before the resistant strain emerged or was more able to establish a latent infection, as has been previously described.[12]

It is difficult to assess the clinical importance of infection with strains of HSV showing altered sensitivity to ACV when the drug is applied topically. After topical administration concentrations of ACV measured in tears varied from 0·07 μg/ml to 465 μg/ml,[13] and in aqueous was around 1·7 μg/ml.[14] Thus it seems that drug concentrations sufficient to inhibit the virus are available at the site of infection even though the strain may have a significantly reduced sensitivity to ACV. The strain resistant to ACV and ganciclovir was sensitive to foscarnet, IDU, and vidarabine, so that a therapeutic alternative, if required, is available.

It thus seems that strains of HSV with reduced sensitivity to ACV exist in the population of patients with herpetic eye disease, but, because of the high ACV levels achieved when applied topically, they respond well to therapy. Virus from subsequent recurrences of HSV disease in such cases may be fully sensitive to ACV.

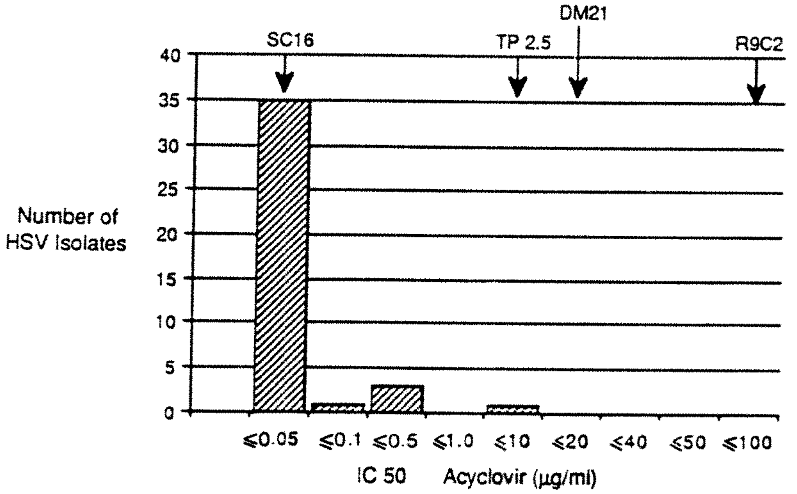

*Figure 2: Distribution of acyclovir $IC_{50}$ values in HSV isolates in patients with ocular infection. $IC_{50}$ values for control strains (see text) are also shown.*

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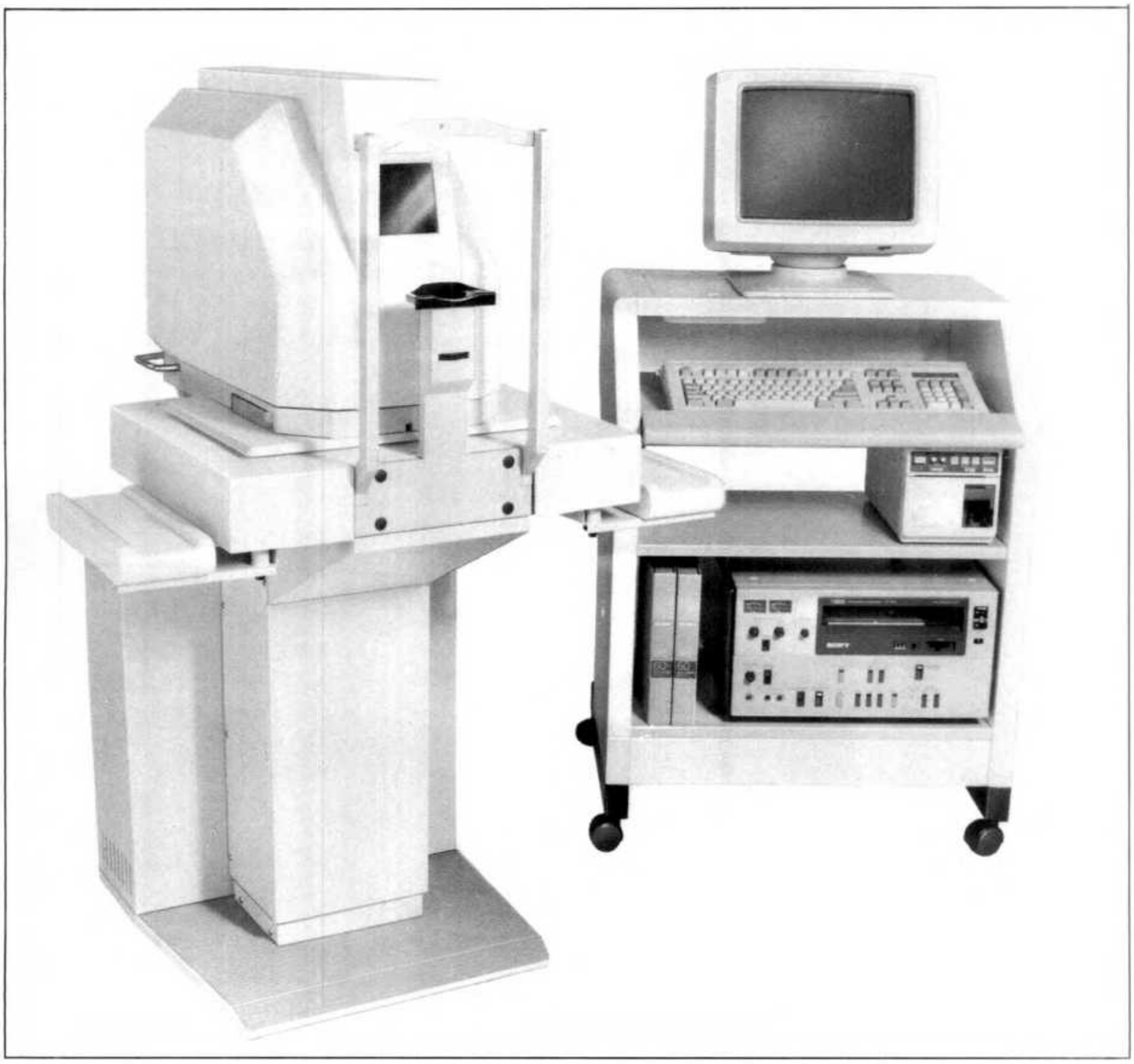

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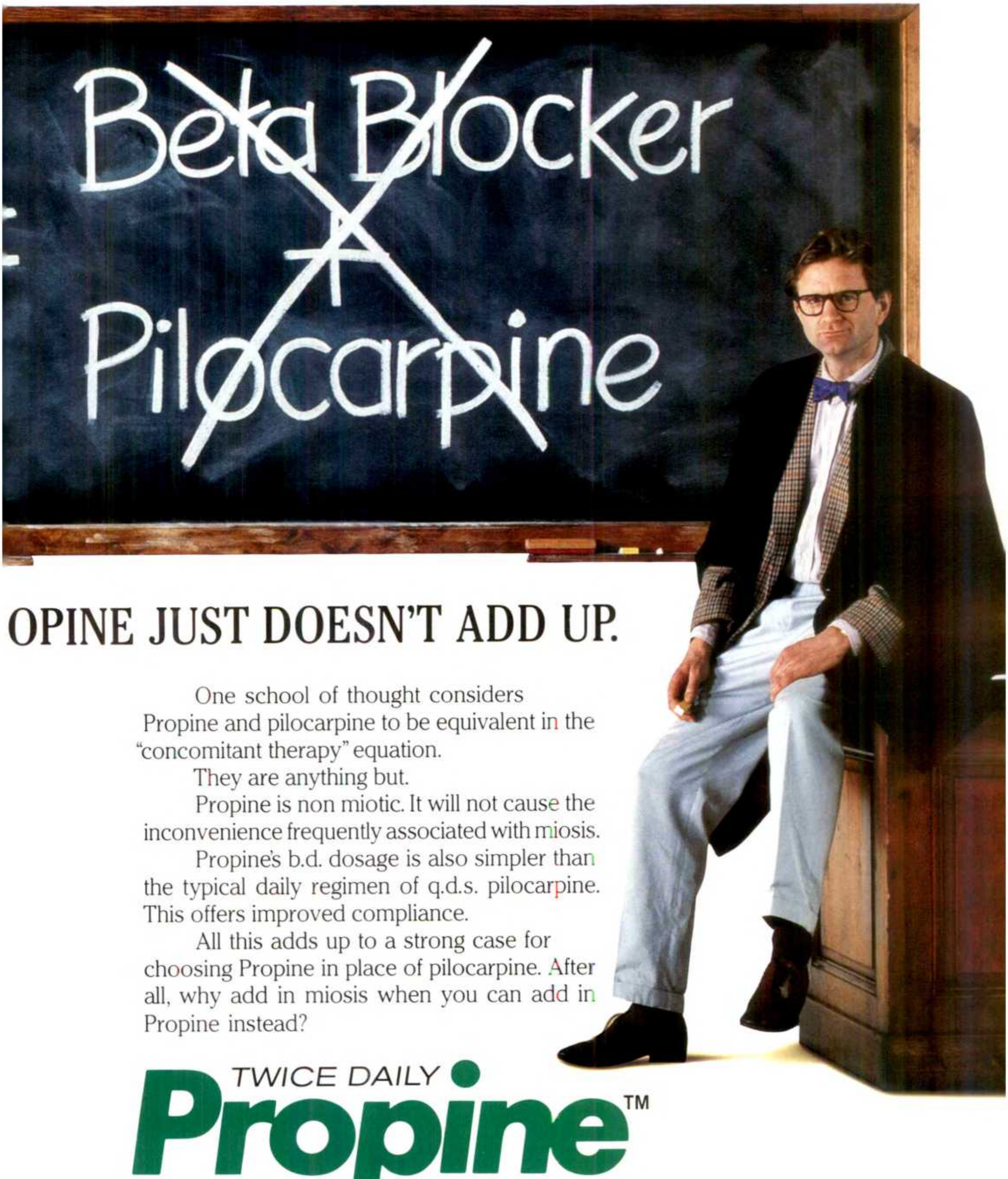
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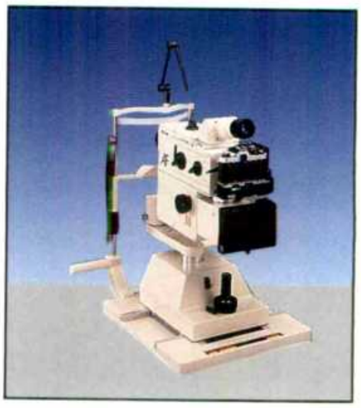

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# Detecting early glaucomatous field defects with the size I stimulus and Statpac

Alan H Zalta, John C Burchfield

**Abstract**

**The influence of stimulus size and normal database on the detection of visual field defects in automated static threshold perimetry (Humphrey Field Analyzer) was investigated in 82 eyes having a diagnosis of normal, glaucoma suspect, or early glaucoma. Using a mathematically derived 'normal' database, which assumes constantly decreasing threshold sensitivities with increasing eccentricity, the size I stimulus showed significantly greater sensitivity than the size III stimulus for detecting small, shallow scotomata in the central visual field. The use of Statpac, which contains an empirically derived, age-related normal database, increased the sensitivity significantly over that of the size III stimulus (with its mathematical model), and to a degree similar to that of the size I stimulus. The results obtained with the size I stimulus were reproducible and independent of the patient's age. This study suggests a potential role for the size I stimulus in evaluating eyes having or at risk of developing early glaucomatous field loss.**

Automated threshold perimetry is a highly standardised, reproducible method of visual field testing which has replaced manual isoptre perimetry as the procedure of choice for detecting and following visual field defects in glaucoma. While the size I (0·25 mm$^2$) stimulus is routinely used for plotting isoptres in manual Goldmann perimetry, the size III (4·0 mm$^2$) stimulus has become the standard for automated threshold field testing. In automated perimetry the size III stimulus offers a larger, more uniform dynamic range and reduces the influence of optical blur as compared with the size I stimulus.[1 2] Furthermore at maximum intensity the size I stimulus is not strong enough to quantify the depth of many defects in automated perimetry.[3]

For all size stimuli on the Humphrey Field Analyzer mathematically derived 'normal' threshold values are used for comparison with the patient's measured threshold values in the determination of defect depth. In this mathematical model the perimeter calculates an expected 'normal' visual field contour for each stimulus size based on a slope equation which assumes a constant decrease in sensitivity for each degree of eccentricity in the visual field.[4] Recently an age related normal database was incorporated into the Humphrey Field Analyzer statistical package, Statpac,[5] for the size III stimulus. In this empirical model the perimeter uses age related threshold values derived from normal subjects as the expected normal visual field contour.

To our knowledge there have been no studies examining the potential uses of the smaller size I stimulus on the Humphrey Field Analyzer. We investigated the sensitivity of the size I stimulus compared with the size III stimulus for detecting early glaucomatous visual field defects in central static threshold perimetry. Both the mathematical model and Statpac's empirical model of normal were used with the size III stimulus for determination of defect depth. The sensitivities of these two models were compared with each other and with that of the size I stimulus. To evaluate further the utility of the smaller stimulus size we also studied the variability of results between initial (first) and subsequent (second) central threshold fields performed with the size I stimulus.

## Materials and methods

Records of all patients seen in the glaucoma referral practice of one of the authors (AHZ) between September 1984 and July 1988 were reviewed. Those patients with eyes having a classification of normal, glaucoma suspect, or early glaucoma and who had undergone central static threshold visual field testing with both size I and size III stimuli were evaluated retrospectively for the presence and density of visual field defects. A defect was defined as a subthreshold locus in the visual field, at least 0·6 log unit in depth, as determined by comparing actual and expected (normal) threshold values at each point in the visual field.

An eye classified as glaucoma suspect had either intraocular pressures greater than 21 mmHg or suspicious asymmetric cupping of the optic nerves. Early glaucoma was defined by intraocular pressure greater than 21 mmHg and either early visual field loss on at least two occasions or early optic nerve damage as confirmed by stereo disc photographs. The visual field defect in early glaucoma consisted of relative nerve fibre bundle defects at least 0·6 log unit in depth involving only a single hemifield and an absence of other optic nerve or chorioretinal disease that might account for the field loss. In the absence of early visual field loss an eye may qualify for the designation of early glaucoma by having either optic nerve cupping at least 15% greater than the contralateral optic nerve or documented progression of cupping by stereo disc photographs.

All central static threshold visual fields were performed with the central 30-2 program on the Humphrey Field Analyzer Model 620 according to the manufacturer's recommendations.[4] A 'full' threshold strategy was used for all initial examination and a 'full from prior' threshold strategy was used for all subsequent examina-

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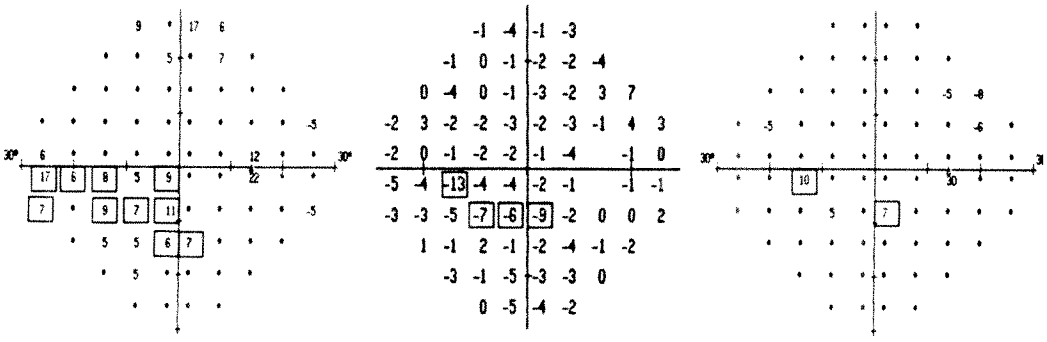

*Figure 1: Defect depth printouts for central static threshold visual fields in an eye with early glaucoma for the size I stimulus using a mathematically derived normal database (left), the size III stimulus using Statpac's empirically derived normal database (middle), and the size III stimulus using a mathematically derived normal database (right). Boxed loci represent ≥6 dB deviations from normal.*

tions. The Humphrey Field Analyzer was updated with all software revisions as they became available and with Statpac.[5]

Exclusion criteria were established to eliminate the influences of learning effect, change in treatment or diagnosis, poor testing reliability, and artefact. We excluded eyes and visual fields with the following conditions: (1) any field which is a patient's first experience with automated threshold testing; (2) pupils that could not be dilated to at least 3 mm in diameter; (3) media opacity reducing visual acuity to less than 20/40; (4) clinically unstable early glaucoma requiring additional ocular hypotensive therapy; (5) consistent low reliability on visual field testing as defined by fixation losses greater than 33%, false positive errors greater than 25%, or false negative errors greater than 25%; and (6) unreproducible edge artefact due to a trial lens rim or an intermittently droopy eyelid or prominent eyelashes. In an effort to minimise artefact the superior and temporal four threshold points at 27° eccentricity were excluded from analysis.

For each eye fulfilling the above criteria three different defect depth printouts were obtained (Fig 1). Numeric defect depth printouts which used mathematically derived 'normal' threshold values were obtained for both stimulus size I and size III fields. In this mathematical model the perimeter uses a slope value of 0·40 dB per degree of eccentricity for the size I stimulus and a value of 0·31 dB per degree of eccentricity for the size III stimulus.[4] Moreover the numeric pattern deviation display on the single field analysis printout, which uses Statpac's empirically derived normal threshold values, was obtained for each stimulus size III field. As seen in Figure 1, defect depth is reported as a positive value for the mathematical model (right and left) and as a negative value for the empirical model (centre).

Defects on these three printouts were classified by the number and depth of contiguous subnormal threshold points. The defect criteria for size were 1, 2, 3, and 4 adjacent loci and for depth were 6, 7, and 8 dB. A field was said to fulfil a given criterion if any defect in the field was of equal or greater size and depth than that criterion.

Variability of results obtained with the size I stimulus was examined in a subgroup of subjects who had undergone more than one central static threshold field with the size I stimulus. Numeric defect depth printouts from the first and second tests on each eye were compared by the aforementioned defect criteria (Fig 2).

A statistical analysis was performed by the Wilcoxon matched pairs signed-rank test.[6] The actual calculations were made by the App-Stat software package for the Apple IIe computer.[7] Although only two separate visual field examinations were performed for purposes of size I and size III stimulus comparisons, three evaluative methods were used, and hence three separate pairwise comparisons were made. Therefore, in an attempt to limit the probability of type I error, statistical significance is claimed at the two-tailed 0·02 rather than 0·05 significance level. Probability values between 0·02 and 0·05 were considered of only marginal significance. The standard two-tailed 0·05 significance level was used for the single pairwise comparison between results from initial and repeat stimulus size I fields.

To determine if age was a confounding variable in the use of the size I stimulus, subjects in

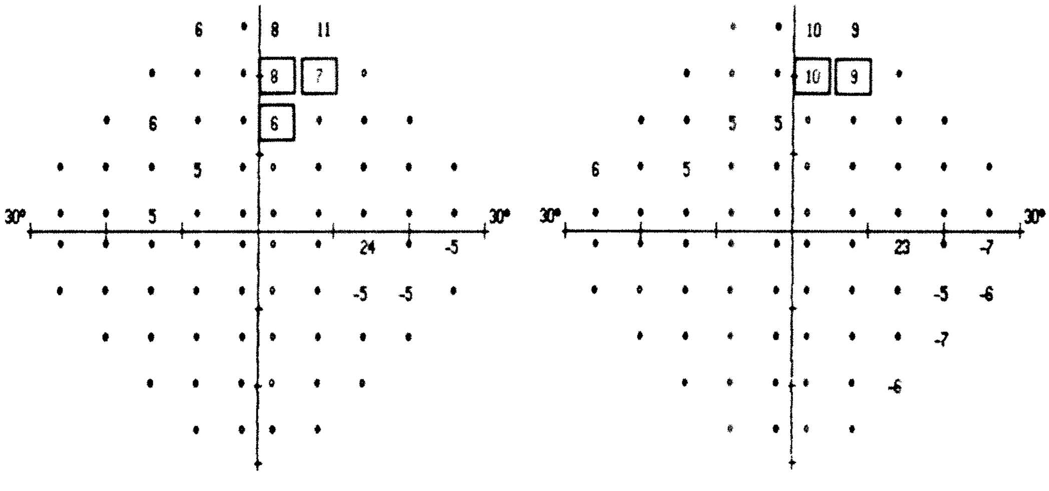

*Figure 2: Defect depth printouts for first (left) and second (right) stimulus size I central static threshold visual fields performed three months apart in an eye suspected of having glaucoma. Boxed loci represent ≥6 dB deviations from normal.*

the glaucoma suspect and early glaucoma populations were divided into two subgroups: those aged 55 and under and those over age 55. A separate analysis with the Mann-Whitney U test[6] was then performed comparing results from the initial stimulus size I fields for these two age groups.

## Results

A total of 82 eyes fulfilled the study criteria and had central threshold fields performed with both the size I and size III stimuli. Of these eyes, 10 were normal, 46 were glaucoma suspect, and 26 had early glaucoma. The mean age (with SD) of all eyes was 50·1 (14·9) years, with mean ages of 35·5 (9·7) years for the normal group, 50·1 (16·2) years for the glaucoma suspect group, and 55·7 (9·8) years for the early glaucoma group. The average length of time (with SD) between performance of stimulus size I and size III fields was 21 (30) weeks (range 0–116 weeks).

Results of overall comparisons of the three evaluative methods are shown in Figure 3 and Table I. For defect depth determination using only the mathematical model the size I stimulus showed significantly greater sensitivity than the size III stimulus for nearly all defect criteria. In the comparison of the two models of defect depth determination with the size III stimulus, Statpac's empirical model showed significantly greater sensitivity than the mathematical model at most defect criteria. With a single exception the sensitivity of the size III stimulus using Statpac's empirical model was not significantly different from that of the size I stimulus for any defect criteria.

In the subgroup of normal eyes there were no significant differences between any of the three evaluative methods for any defect criteria with a single exception. For defects consisting of a single 6 dB locus, the size III stimulus with the empirical model was more sensitive than the size III stimulus with the mathematical model.

Of the 82 eyes 42 had second central threshold fields performed with the size I stimulus. Diagnostically, four eyes were normal, 24 were glaucoma suspect, and 14 had early glaucoma. The average length of time (with SD) between initial and subsequent size I stimulus fields was 22 (27) weeks (range 0–109 weeks). Comparison of results from initial and repeat stimulus size I fields revealed no significant differences ($p>0·05$) in sensitivity between the two tests for all criteria of defect size and depth.

In the glaucoma suspect group there were 20 eyes of patients over age 55 and 26 eyes of patients aged 55 or younger. In the early glaucoma group there were 13 eyes of patients over age 55 and 13 eyes of patients aged 55 or younger. For fields performed with the size I stimulus a comparison of results between the two age groups revealed no significant differences for all defect criteria for both diagnostic groups.

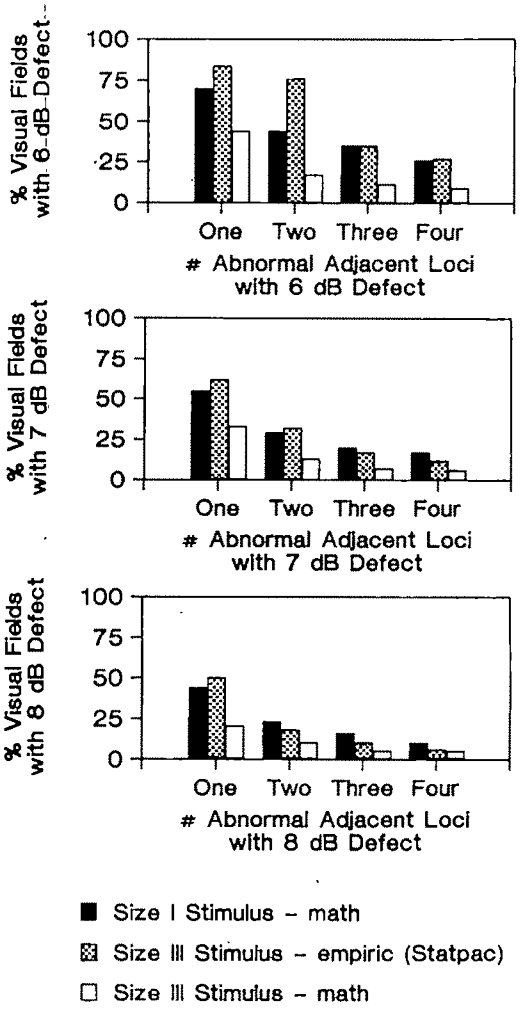

*Figure 3: Percentage of visual fields fulfilling defect criteria for the size I stimulus using a mathematically derived normal database (size I stimulus-math), the size III stimulus using Statpac's empirically derived normal database (size III stimulus-empirical), and the size III stimulus using a mathematically derived normal database (size III stimulus-math).*

## Discussion

The psychophysical effects of the different-sized stimuli used in manual Goldmann perimetry and automated threshold perimetry have been previously studied.[2,9] However, little research has been done on the clinical applications of nonstandard stimuli in automated perimetry. Gramer *et al*[10] compared the stimulus size I and size III in 12 eyes and the stimulus size III and size V in 18 eyes with glaucoma. They found that when 'using large test targets, small scotomata can be overlooked and identified field defects appear smaller and less deep'. More recently Wilensky *et al*[11] demonstrated the potential usefulness of the larger size V (64 mm$^2$) stimulus in testing eyes with advanced glaucoma. To the best of our knowledge there have been no studies examining the clinical utility or sensitivity of the size I stimulus on the Humphrey Field Analyzer.

When a mathematically derived 'normal' database is used in the determination of defect depth, we discovered that the size I stimulus shows significantly greater sensitivity in detecting, small, shallow scotomata than the size III stimulus. This finding may be explained by the concept of spatial summation. It is well known that because of spatial summation a larger stimulus is more easily seen than a smaller stimulus of the same luminance.[2,3] The increased sensitivity of the size I stimulus may be due to stimulation of a smaller retinal receptive field with a consequent reduction in spatial summa-

TABLE I *Overall comparisons of sensitivity of size I and size III stimuli using mathematically and empirically derived normal databases**

| *Defect criteria, size (adjacent loci) × depth (dB)* | *Probability values*<br>*I-math v III-empiric* | <br>*I-math v III-math* | <br>*III-empiric v III-math* |
|---|---|---|---|
| 1×6 | 0·02 | 0·002 | 0·0001 |
| 2×6 | NS | 0·0007 | 0·0008 |
| 3×6 | NS | 0·0009 | 0·0002 |
| 4×6 | NS | 0·009 | 0·001 |
| 1×7 | NS | 0·007 | 0·0001 |
| 2×7 | NS | 0·01 | 0·001 |
| 3×7 | NS | 0·02 | 0·01 |
| 4×7 | NS | 0·04 | 0·03 |
| 1×8 | NS | 0·002 | 0·0001 |
| 2×8 | NS | 0·01 | 0·04 |
| 3×8 | NS | 0·01 | NS |
| 4×8 | NS | NS | NS |

*I-math indicates size I stimulus using mathematically derived normal database; III-empiric indicates size III stimulus using Statpac's empirically derived normal database; and III-math indicates size III stimulus using mathematically derived normal database. NS, not significant.

tion, as compared with the size III stimulus. The principle is the converse of that of using the larger size V stimulus in advanced glaucoma to map threshold values in areas of the visual field unresponsive to the standard size III stimulus. In this case the smaller size I stimulus detects subthreshold responses in areas of the visual field mapped as normal by the less sensitive size III stimulus.

The size III stimulus, however, does have certain diagnostic advantages. It offers a larger and more uniform dynamic range than the size I stimulus, particularly in the less sensitive peripheral field, where spatial summation is inherently greater.[2,8] Also, by extending the dynamic range, the size III stimulus 'makes it possible to record the sensitivity distribution in areas of maximal reduction of sensitivity'.[2] In screening for early glaucomatous visual field loss, however, one is not examining the peripheral field nor attempting to quantify severe abnormalities in the central field. Rather, one is attempting to detect shallow paracentral scotomas. Hence a more desirable psychophysical property in such an application is maximal sensitivity in the central field. In threshold field testing of glaucoma suspects or eyes with early glaucoma, increased dynamic range with the size III stimulus is not of real practical value. In fact the smaller size I stimulus, which excites a lesser degree of spatial summation, may be a more logical stimulus choice. This reasoning is supported by the greater sensitivity of the size I stimulus than the larger size III stimulus seen in this study.

What is the clinical significance of the increased sensitivity of the size I stimulus over the more commonly used size III stimulus when a mathematically derived 'normal' database is used in determination of defect depth? Does it merely create false positive defects, or does it provide data which can be used in following a patient's clinical course or in making a decision to initiate treatment? In the subgroup of normal eyes there were no significant differences between results from the size I and III stimuli for any of the defect criteria. This supports our belief that the sensitivity of the size I stimulus is real and not simply derived from the creation of false positive defects. Furthermore, repeat field testing with the size I stimulus showed that these small, shallow scotomas were reproducible and independent of the patient's age. We believe that the increased sensitivity of the size I stimulus provides clinically useful information for evaluating and following up patients at risk of developing, or who already have, early glaucomatous visual field loss.

In addition, the sensitivity of the size III stimulus using an empirical model closely matched that of the size I stimulus using a mathematical model. To explain this finding we must assume that the increase in sensitivity resulting from use of the smaller size I stimulus is similar in degree to that of using an empirically derived database with the size III stimulus. Heijl *et al*[12] have shown that there is significant location dependent variability of threshold values across the central visual field for the standard size III stimulus on a Humphrey Field Analyzer. This normal variability is not accounted for by the slope equation in the mathematical model but is inherently accounted for by the age related empiric database. Perhaps the use of an empirically derived normal database with the size I stimulus might further increase the sensitivity of threshold perimetry in glaucoma suspects and patients with early glaucoma by combining the benefits of both a smaller stimulus size and a more accurate approximation of expected threshold values.

When a smaller target size is used in perimetry, there is a greater influence of light diffusion caused by opacities of the media.[2] In this study we excluded all eyes having media opacity which reduced visual acuity to less than 20/40. In the presence of significant media opacity there may be a high level of background noise on field testing with the size I stimulus. Larger stimulus sizes may provide more useful information when the transparency of the dioptic media has suffered.[2]

The current set of standard parameters used in automated threshold perimetry provide flexibility and sensitivity in a broad range of applications. While the size III stimulus may be appropriate for routine perimetry, our results suggest a role for the size I stimulus in screening for early glaucomatous visual field defects. As this study and Wilensky *et al*[11] have shown, certain specialised applications of threshold perimetry might be better served by nonstandard parameters such as the size I or size V stimulus. As more of these specialised applications are discovered, and with the development of the corresponding perimetry software, it may be possible, through the selection of different stimulus sizes, to tailor visual field tests specifically to a patient's clinical status in order to obtain the most useful information for diagnosis and treatment.

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The authors have no direct or indirect commercial or proprietary interest in the Humphrey Field Analyzer or any other product mentioned in this report.

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# Biomicroscopic examination of the ocular fundus with a +150 dioptre lens

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## Abstract

**This article describes the design of a +150 dioptre compound lens for biomicroscopic examination of the fundus. To compare the lens with other fundal examination techniques a method is described for measuring the magnification and vertical angle of view of the various examination lenses. By this method the +150 dioptre lens is shown to have an angle of view of 60°. This is similar to that of the indirect ophthalmoscope when used with a 20 dioptre lens which has an angle of view of 57°. However, the magnification of the +150 dioptre lens is greater at ×5·2 compared with ×3·0 for the indirect ophthalmoscope. The practical applications of the lens are discussed. In comparison the field of view of the +78 and +90 dioptre lenses are 37° and 29° respectively. The +150 dioptre lens has proved a useful adjunct enabling a rapid global screening of the ocular fundus on the slit-lamp before examining any particular area of interest in more detail.**

Since Helmholtz[1] first examined the fundus with a direct ophthalmoscope in 1851 there has been a great diversity of lenses and tools to examine it.[2-5] El Bayadi[6] first reported using a high powered convex lens, +56·8 dioptres, with the slit-lamp microscope in 1953. With the improvements in the quality of optical manufacture in the 1980s the double aspheric +90 dioptre lens has become the standard lens to conduct biomicroscopy of the fundus. The recent introduction of the +78 dioptre lens further emphasises the popularity of using a non-contact lens. The good quality stereomagnified view produced in this way is especially suited to examining the optic disc and posterior pole. This often avoids the need for a fundal contact lens examination, so reducing examination time and the patient's discomfort.

However, the +90 dioptres lens's very advantage of a magnified image limits the field of view. This may cause a more peripheral or global lesion to be overlooked. In addition when using the +90 dioptre lens media opacities can seriously reduce the retinal image quality. To overcome these difficulties many may turn to the head mounted indirect ophthalmoscope, with a wider global field of view and far less trouble from media opacities. Thus there is a need for a non-contact fundal lens which produces a much wider field of view. This can be achieved by using a higher power examination lens.

This article describes a +150 dioptre compound lens which is used with the slit-lamp in a similar fashion to the +90 dioptre lens. The field of view obtained with the +150 dioptre lens is compared with that obtained by variety of other fundal examination techniques.

## Lens design

In order that light from a large field of view may pass through a single fundal examination lens it has to be large. However, the very small (6·8 mm) radius of curvature of a +150 dioptre single lens limits its overall size. Together with the marked peripheral aberrations of such a lens, the overall useful field of view would be limited. This well known difficulty is encountered in microscope and telescope eyepieces. In these instances the problem is overcome by using two separated positive lenses, so forming the standard Huygens eyepiece.[7] The field lens is placed at the focus of the main eye lens to increase the field of view but leaves the magnification unaltered. If, however, the two lenses are moved closer together the dioptric power of the combination increases, while the lens still maintains the advantages of increased field of view and reduced aberrations of the Huygens lens.

The +150 dioptre lens is thus produced by two +80 dioptre double convex 11 mm diameter glass lenses separated by a 5 mm air gap (Fig 1). The optics are in principle identical to those of the 90 D (Fig 2). A possible disadvantage in using a combination lens is the increased amount of reflections from the optical surfaces. This is minimised by having the lenses coated with a multilayered antireflecting coat. In addition an oblique light source is used, and as a consequence no significant reflections from the optical surfaces are encountered. The overall size of this combination lens makes it pleasantly comfortable to hold and easy to handle.

The +150 dioptre lens together with the +90 and +78 dioptre lenses share the disadvantages of the inverted indirect view, and liability to fatigue the user, of a hand held lens. These lenses also share the disadvantage of having a slit

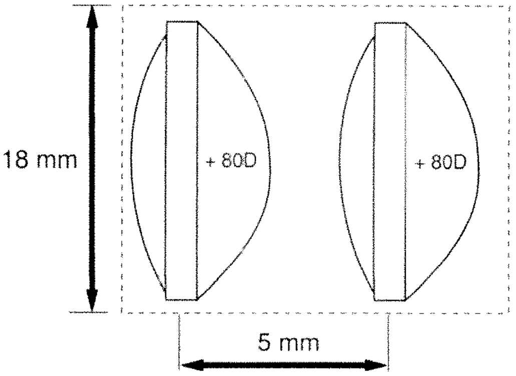

*Figure 1: Optical construction of the lens.*

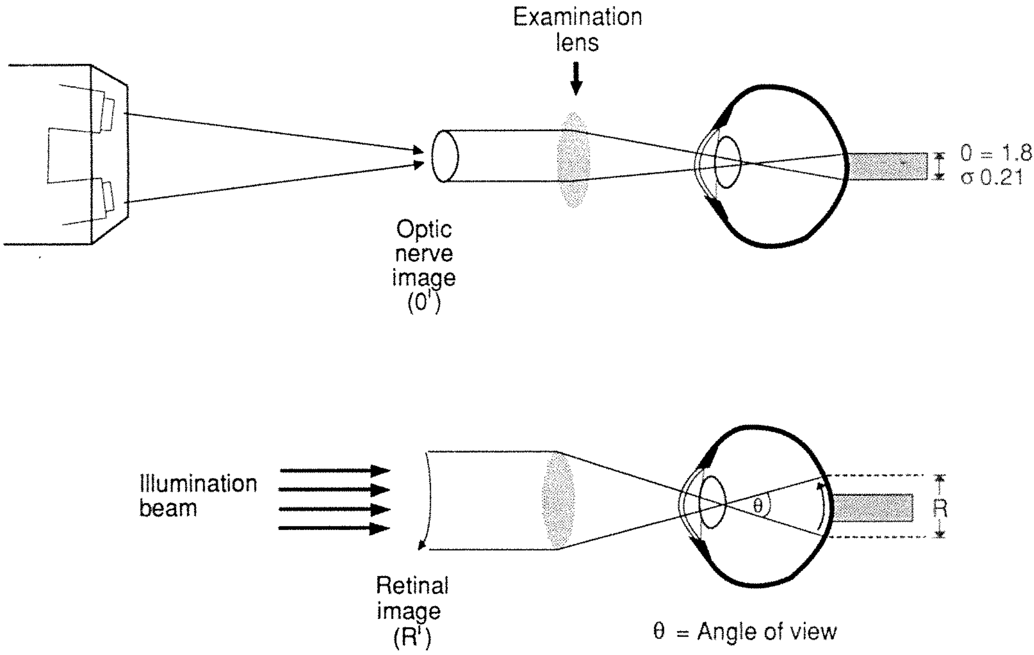

*Figure 2: To measure the angle of view (θ) of the various examination lenses two measurements in mm were made: (a) the vertical size of the optic nerve image O'; (b) the maximum vertical size of the curved retinal image R' generated by the illumination beam.*

illumination rather than the 360° illumination of the indirect ophthalmoscope.

EVALUATION OF FIELD OF VIEW

To avoid the complexity of using a theoretical calculation on the complex optical system created by the slit-lamp, examination lens, and the eye, a clinically based method was devised to measure the angle of view. The size of the optic disc has been studied in 200 post-mortem eyes by Straatsma *et al*[8] and found to vary within small limits. The vertical size was found to be 1·86 mm (SD 0·21). This vertical diameter of the optic disc was used as a scale from which the vertical angle of view could be calculated (Fig 2).

Twenty-one emmetropic patients were examined by the author. The pupils were dilated with tropicamide 1·0% and phenylephrine 10%. The fundus was examined by the following methods: slit-lamp based +150 D, +90 D, +78 D, Hruby lenses, and fundal contact lens; indirect ophthalmoscope with +14 D, +20 D, +30 D, and the Hamblin 2000 direct ophthalmoscope. Measurements of the vertical size of the optic disc were made together with the maximum vertical field of view illuminated at any one moment. For the +150, +90, and +78 dioptre lens these measurements were made on the image formed between the lens and the slit-lamp. The scale of a 1000×0·1 mm graticule microscope slide was superimposed on this optic disc image and the maximum diameter of the optic disc recorded.

In a similar fashion a standard millimetre ruler was used to measure the image produced between the lens and the indirect head piece. However, with the Hruby and fundal contact lenses no image is produced between the lens and the slit-lamp. Therefore the graticule scale could not be superimposed on the optic disc image. Instead a Haag-Streit slit-lamp with a scaled vertical slit-lamp illumination beam was used. The slit-lamp's inbuilt millimetre slit length scale was checked and compensated for with the graticule microscope slide. The optic disc size and maximum vertical field of view could then be measured with the illuminating beam. With the direct ophthalmoscope the number of disc diameters in the vertical field of view was estimated by observation. The ratio of the image size of the optic disc to the actual optic disc size will be the same as the maximum vertical measurement of retina in view to its actual measurement in the eye (Fig 2). Thus

$$\text{Vertical distance of retina in view } R=\frac{R'\times O}{O'}$$

As the retina and its image are both curved, the vertical measurement made represents a chord across the posterior pole of the eye. With Gullstrand's schematic eye[9 10] with an inner equatorial diameter of 24·1 mm,[11] a scale drawing of the eye was made on 1 mm squared paper. Though the human eye is an oblate spheroid,[12] the posterior pole was assumed to be spherical. The chord could then be drawn in and the angle of view (θ) could be read off with a protractor. The magnification of the image is calculated by dividing the mean optic disc image size by 1·86 (the mean vertical disc diameter) and multiplying this by the slit-lamp magnification, if appropriate.

## Results

The mean and 95% confidence limits of the measurements taken are tabulated in Table I. The +150 dioptre lens was found to have the largest vertical field of view of 60°. This was closely followed by the indirect ophthalmoscope used with the 20 dioptre lens, with a field of view of 57°. The +90 dioptre lens field of view was smaller at 37° and the +78 dioptre lens at 29°. The fundal and Hruby lenses were more prone to have their field of view limited by the patient's pupil than the others. For the fundal lens the field of view was 20° and the Hruby lens 17°. However, the Hruby and fundal lenses produced the maximum magnification of all the lenses of ×11·7 and ×11·2.

TABLE I *Angle of view and magnification of various examination lenses*

| *Lens type* | *Number of observations* | *Disc size, mm* | *95% Confidence limits, mm* | *Illumination size, mm* | *Overall magnification* | *Angle of view, degrees* | *95% Confidence limits, degrees* |
|---|---|---|---|---|---|---|---|
| *Indirect ophthalmoscopy* | | | | | | | |
| Nikon 20 D | 15 | 5·5 | 0·3 | 45 | ×3·0 | 57·1 | 3·8 |
| Nikon 30 D | 9 | 4·8 | 0·33 | 34 | ×2·6 | 48 | 4·1 |
| Nikon 14 D | 6 | 8 | 0 | 52 | ×4·2 | 42·7 | 0 |
| *Slit-lamp examination lenses* | | | | | | | |
| 150 D | 21 | 0·96 | 0·09 | 8 | ×5·2 | 60 | 6·4 |
| Volk 90 D | 21 | 1·44 | 0·12 | 8 | ×7·7 | 37 | 3·1 |
| Volk 78 D | 14 | 1·79 | 0·13 | 8 | ×9·6 | 29 | 2·2 |
| Haag-Streit fundal contact lens | 13 | 2·08 | 0·26 | 6·36 | ×11·2 | 20 | 3·5 |
| Haag-Streit Hruby lens | 12 | 2·17 | 0·36 | 5·9 | ×11·7 | 17 | 2·2 |
| Hablin 2000 ophthalmoscope | 8 | 1·25 Disc diameters | | | | 8 | – |

## Discussion

The +150 dioptre combination lens is used in a similar way to the +90 D on the slit-lamp. The combination lens is held a little closer to the cornea, 10 mm compared with the +90 dioptres lens's 15 mm. Though the best images are obtained with a dilated pupil, as is the case with the +90 dioptre lens, it is possible to obtain a satisfactory view with pupils as small as 3 mm in diameter. The illuminating beam should be at its minimum intensity and set at an angle of 20° to the objectives, unlike the virtually coaxial beam needed with the +90 D. The beam width can be set to 15 mm before the image quality deteriorates, compared with 12 mm with the +90 dioptre lens. This also increases the immediate field of view. The oblique light source also produces a relief to raised areas. The inverted aerial image in front of the lens is viewed in the usual way with the slit-lamp.

The view obtained with the +150 dioptre combination lens is similar to that of the indirect ophthalmoscope, both having a field of view of approximately 60°. However, the aerial image of the +150 dioptre lens is further magnified by the slit-lamp to produce an overall magnification of ×5·2 compared with ×3·0 for the indirect ophthalmoscope. This allows greater detail to be extracted from the image. The magnification can be further altered by the variable slit-lamp optics. The Galilean optics of the latest Haag-Streit slit-lamp are particularly suited to this. With the +150 dioptre lens an image similar to that of the indirect ophthalmoscope and the +78 dioptre lens can be obtained by alternating only the slit-lamp magnification.

By decentring the lens, utilising the large prismatic effect of the high power combination lens, and if necessary asking the patient to move his eye, it is possible in a patient with well-dilated eyes to view out to the ora serrata. By working one's way round the eye, in a similar manner to 'spinning' the three-mirror contact lens, the peripheral retina can be examined stereoscopically. Comparing previous fundal photographs with the patient's fundus and drawing a retinal drawing is facilitated by having both patient and observer comfortably seated at the slit-lamp. The good stereopsis and wide field of view allow excellent visualisation and estimations of the size and position of retinal tears and indents after retinal detachment surgery. The global view allows the overall pattern of the retinopathy to be viewed in its entirety instead of having to build up a mental picture while viewing small areas of the fundus. Media opacities disturb the retinal image to a lesser extent than with the +90 or +78 dioptre lens, and the +150 dioptre lens is almost as good in this respect as the indirect ophthalmoscope.

The lower magnification increases the depth of field, enabling excellent visualisation to be obtained of that most difficult of structures to view, the vitreous. This is further enhanced by the oblique light source which is scattered by the vitreous structures and opacities to produce a well defined image.

Biomicroscopy with the +150 dioptre lens produces a retinal image with an overall magnification of ×5·2 and with a wide angle of view of 60°. This is comparable to that of the indirect ophthalmoscope being used with a +20 dioptre lens, which produces an angle of view of 57°, but the magnification is lower at ×3·0. The +150 dioptre lens is particularly useful in screening the eye for pathology. Areas of particular interest can then be viewed easily at higher magnification by changing the examination lens to the +90 dioptre (×7·7) or +78 dioptre (×9·6) lens.

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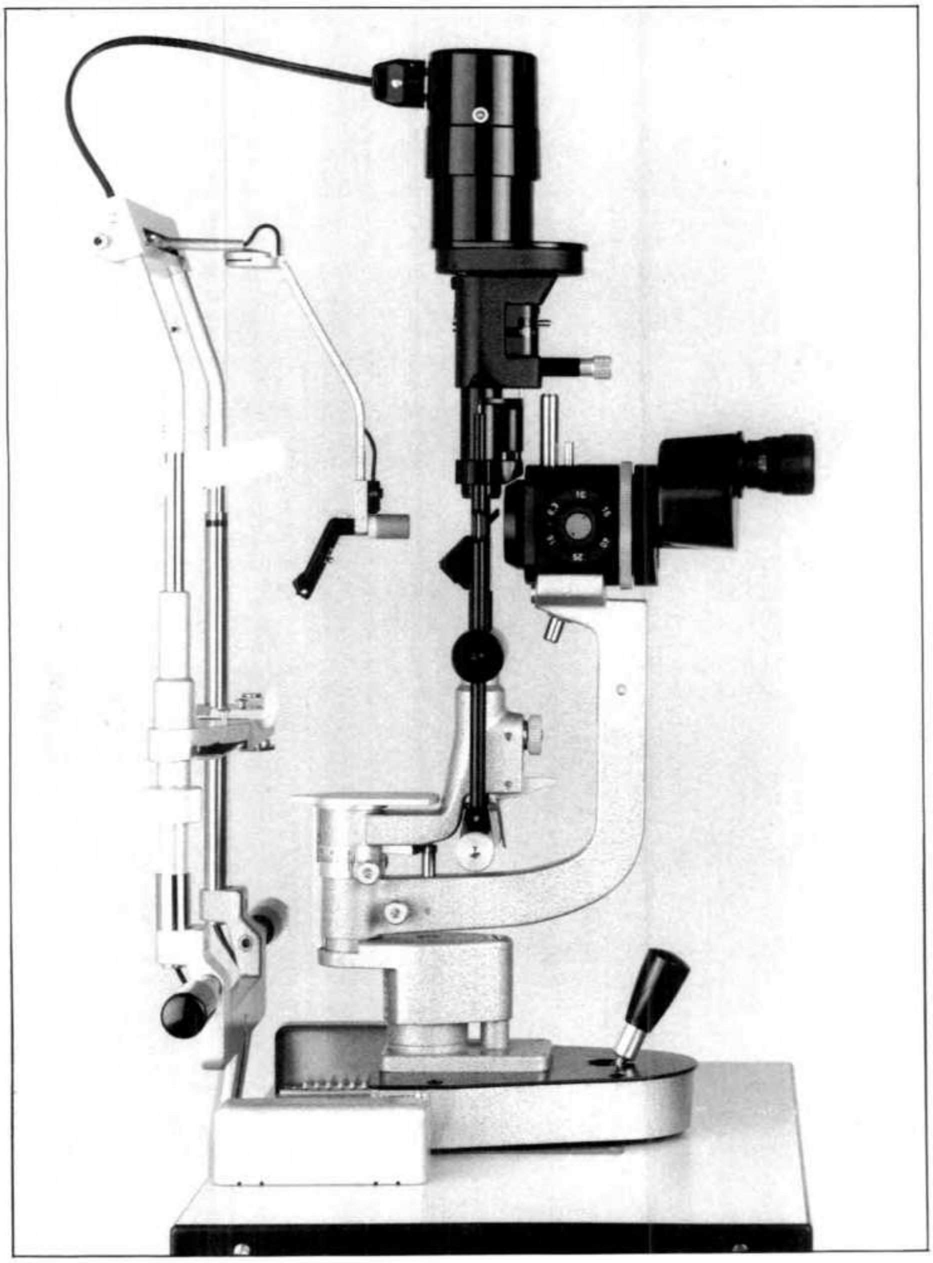

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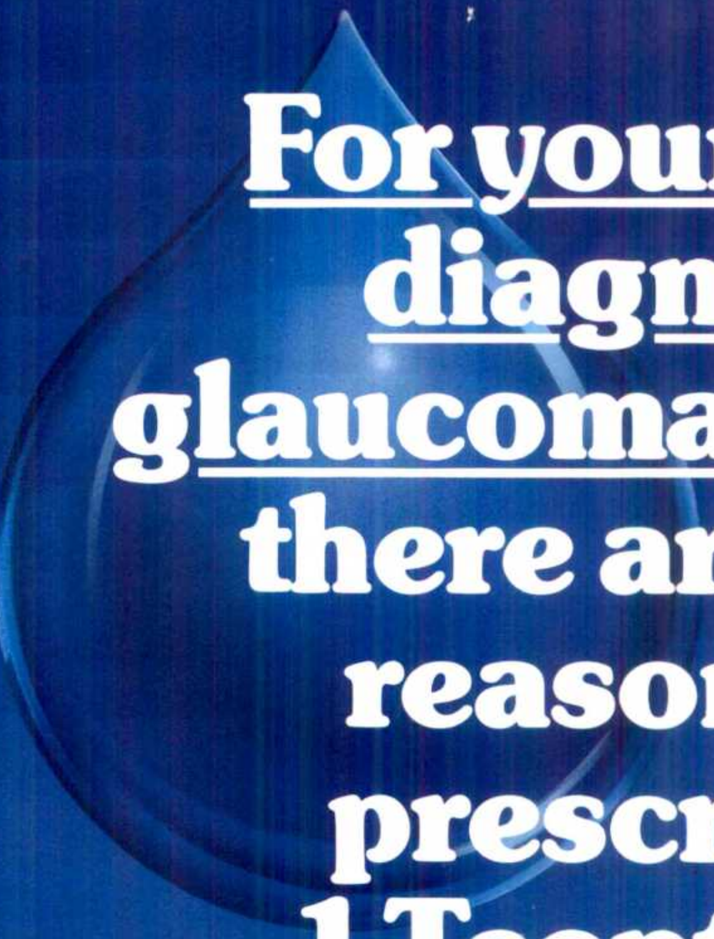

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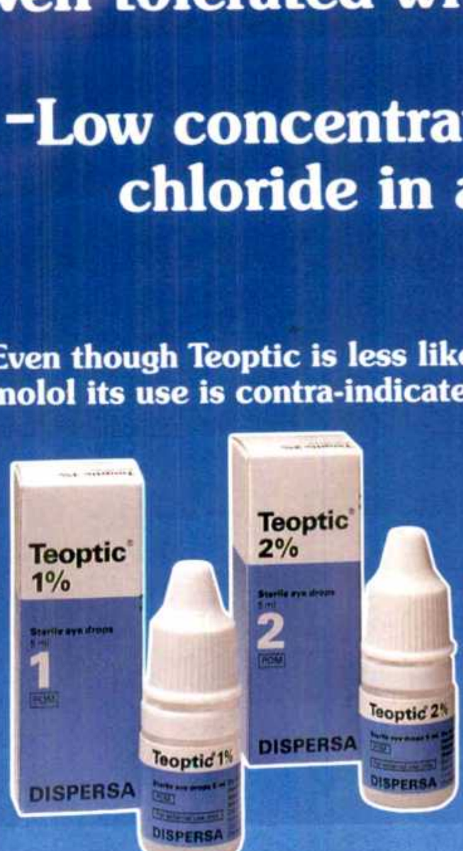

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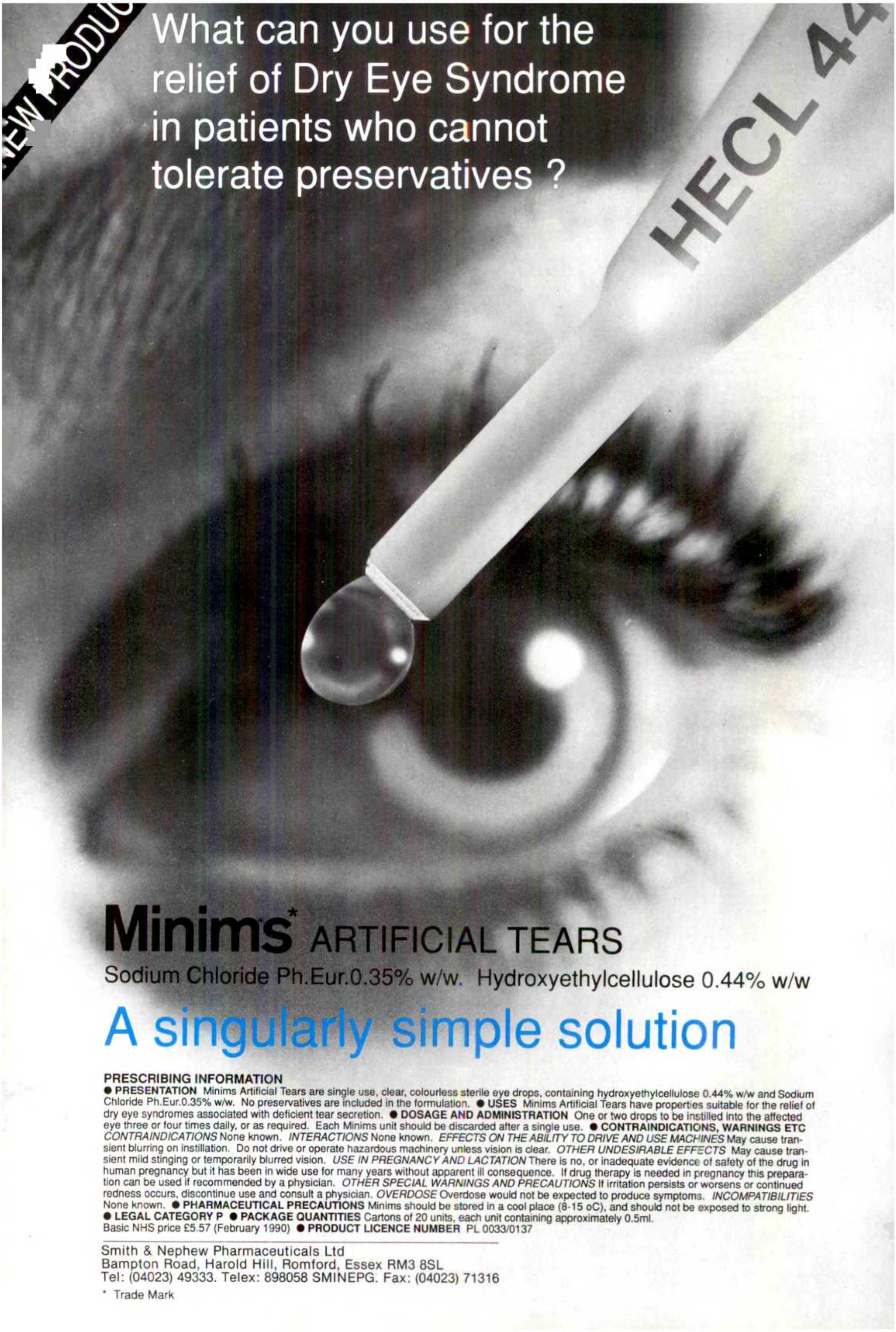

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# Optic nerve hypoplasia and astigmatism: a new association

Sabah M Zeki

**Abstract**

**Thirty-one patients with optic nerve hypoplasia (ONH) or septo-optic dysplasia and two patients with segmental ONH underwent retinoscopy. The results were compared with those of 20 normal subjects. There was a higher prevalence of astigmatism in the patients than in the controls. Two patients with segmental ONH had no evidence of astigmatism. The association of astigmatism with ONH has not hitherto been reported. The close association of ONH with astigmatism highlights the importance of performing careful retinoscopy in children with ONH or septo-optic dysplasia in order to identify and correct errors of refraction, thereby optimising visual function and diminishing the likelihood of the development of superadded amblyopia.**

Optic nerve hypoplasia (ONH) is a non-progressive congenital abnormality of one or both optic nerves associated with a diminished number of axons.[1 2] It causes various degrees of defective vision ranging from minimal visual impairment to total blindness. Bilateral disease has increasingly been reported as being commoner than unilateral disease.[3-5] ONH often does not represent simply an isolated ocular anomaly. Several clinically important endocrine and central nervous system abnormalities are now recognised as associated conditions[4 6 7] as well as a large number of systemic abnormalities.[1 5 8] Lambert *et al*[5] have produced a useful comprehensive review of the literature on ONH. Segmental ONH[9] and tilted discs in association with ONH[10] have also been described.

## Patients and methods

Thirty-three patients with ONH underwent retinoscopic examination. Four of them had unilateral ONH and two had unilateral segmental ONH. They had been identified from the inpatient disease index of the Royal Hospital for Sick Children (RHSC) and the RHSC Outpatient Department diagnostic index maintained by the consultant staff. Two of the patients were identified in the eye department at Aberdeen Royal Infirmary and were also included in the study (with permission of the head of the department). Moreover, two patients were referred to the author during the period of the study.

All patients with non-segmental ONH also had disc-macula/disc diameter ratio of over 3·1 which is characteristic of the condition.[11 12] Only one patient (no. 16) showed no double ring sign. However, she had severe constriction of the visual fields, hypothalamic obesity, cerebral palsy, and mental retardation. Comparing the diameter of her optic discs with the width of the slit-lamp beam, on contact lens biomicroscopy, showed her optic discs to have 1 mm diameter (average disc diameter in normal persons is 1·42 (SD 0·24) mm).[13] Eighteen normal children from a local primary school were also tested (after the parents had consented to their child's being refracted), and two normal adult volunteers were refracted to make a total number of 20 normal subjects. All patients and control subjects received one drop of 1% cyclopentolate to induce cyclolegia in each eye half an hour before retinoscopy.

Retinoscopy was performed by using the right eye of the examiner to test the right eye of the patient and the left eye of the examiner to test the left eye of the patient. It was performed from a distance of two-thirds of a metre and as close to the visual axes of the patients as possible. The patients and the normal subjects were encouraged to look at a target positioned 6 m away. Retinoscopy was performed on all patients and normal subjects by the author.

For the purpose of statistical analysis of data the mean for the two eyes was taken as the datum value for a subject unless only one eye had been assessed, in which case the value for that eye was taken. The rationale for this type of analysis has been described previously.[14 15]

## Results

The normal group was divided into two according to age. The first group comprised nine subjects aged 4 to 7, and the second group comprised 11 normal individuals between the ages of 8 and 35. The two groups were compared. There was no statistically significant difference between the two age groups in the normal control group either with regard to the total spherical power (*t* test, p>0·5) or astigmatism (*t* test, p>0·5).

The correlation coefficient for the age variation of the total spherical power in the two groups of normal subjects was not significant (Pearson correlation coefficient, p>0·1). The mean total spherical power of the right eye in the younger group was +2·35 dioptres, while the mean of the total spherical power of the right eye in the older group was +2·20 dioptres. The mean astigmatism in the younger group was 0·14 dioptre in the right eye, while it was 0·20 for the right eye in the older group. The mean astigmatism in the left eye was 0·17 dioptre in the first group and 0·20 in the second.

The correlation coefficient between the mean total spherical power and age among the patient group was not significant (Pearson correlation coefficient, p>0·1).

Astigmatism was common in the 58 eyes of patients with ONH (apart from the two patients

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TABLE I *The findings of retinoscopy in the patient group*

| Patient | Age (years) | Sex | Total spherical power OD | Total spherical power OS | Astigmatism OD | Astigmatism OS |
|---|---|---|---|---|---|---|
| 1 | 6 | F | 2·25 | 2·5 | 1·5 | 0 |
| 2 | 4 | M | 1·75 | 0·75 | 1·5 | 0·5 |
| 3 | 3 | F | 1·62 | 1·12 | 0·25 | 0·75 |
| 4 | 4 | M | 3·75 | 2·87 | 0·5 | 0·75 |
| 5 | 3 | F | −4·62 | −3·37 | 0·75 | 1·25 |
| 6 | 4 | F | 6·25 | 7 | 2 | 1·5 |
| 7 | 4 | F | −2·5 | −3·25 | 2 | 3·25 |
| 8 | 4 | F | 3·12 | 3·12 | 0·25 | 0·25 |
| 9 | 8 | M | 2 | 2·12 | 0·5 | 1·75 |
| 10 | 17 | M | −2·25 | −0·87 | 6 | 3·25 |
| 11 | 21 | F | 0·12 | 0·00 | 1·75 | 1·5 |
| 12 | 1 | F | 4·25 | 4·75 | 1 | 0·5 |
| 13 | 19 | F | 1·37 | 2·62 | 0·75 | 2·75 |
| 14 | 11 | M | 1·25 | 1·12 | 4 | 4·25 |
| 15 | 3 | M | 1·62 | 0·5 | 1·25 | 1·5 |
| 16 | 2 | M | 2·25 | 2·12 | 0·5 | 0·25 |
| 17 | 7 | M | 3·37* | 3·5 | 0·25* | 0·5 |
| 18 | 15 | F | −1·37 | −1·37 | 4·25 | 4·25 |
| 19 | 8 | F | 2·12* | 2·67 | 0·25* | 0·75 |
| 20 | 2 | M | 2·5 | 2·5 | 1·5 | 2 |
| 21 | 16 | M | 1·25 | 0·75 | 0·5 | 0·5 |
| 22 | 7 | F | 5* | 3·75 | 0·00* | 2 |
| 23 | 6 | M | 1·12 | 2·37 | 2·75 | 2·25 |
| 24 | 14 | M | 0·5 | 0·37 | 2·5 | 2·25 |
| 25 | 7 | M | 1·5 | 2·5 | 1·5 | 2·5 |
| 26 | 7 | M | 0·25 | −2·25 | 1·25 | 2·25 |
| 27 | 26 | F | 1·75 | 1·75 | 0·5 | 0·5 |
| 28 | 4 | M | 4·5 | 5 | 0·5 | 1 |
| 29 | 19 | M | 1·5 | 2·37 | 0·5 | 0·25 |
| 30 | 4 | M | 2 | 2·62 | 1 | 1·75 |
| 31‡ | 9 | F | 3 | 3 | 0·00 | 0·00 |
| 32 | 43 | F | † | 0·5 | † | 0·5 |
| 33‡ | 22 | F | 1·75 | 1·75 | 0·00 | 0·00 |

*Findings in eyes which were deemed not to have ONH
†This patient's right eye had high myopia, dense amblyopia, and a visual acuity of light perception only.
‡Patients with segmental ONH.

with segmental ONH, who had no astigmatism) when compared with the normal subjects (Table I). This was statistically highly significant (Mann-Whitney test and Welch's test, $p<0{\cdot}001$). The mean astigmatism in the right and left eyes with ONH was 1·53 and 1·52 dioptres respectively. The proportion of patients with ONH who had astigmatism greater than 0·5 dioptre was 62% in the 27 right eyes with ONH and 66·5% in the patient group's 31 left eyes with ONH (apart from the two patients with segmental ONH). Only one subject in the normal group had astigmatism of greater than 0·5 dioptre in her left eye (0·75 dioptre). Furthermore, one patient (no. 26) who had left unilateral ONH showed no astigmatism in the right eye, while in the eye with ONH (left eye) he had 2 dioptres of astigmatism. Of the other three patients with unilateral optic nerve hypoplasia one had a highly myopic blind eye, and her other eye had ONH with astigmatism of 0·5 dioptre. Of the remaining two patients one had 0·25 dioptre astigmatism in the normal eye (but she had a 0·75 dioptre of astigmatism in the eye with ONH), and the last patient with unilateral ONH had 0·25 dioptre of astigmatism in the normal eye and an 0·5 dioptre in the eye with ONH.

TABLE II *Visual acuities with and without correction*

| Patient | Unaided OD | Unaided OS | Aided OD | Aided OS |
|---|---|---|---|---|
| 1 | * | * | * | * |
| 2 | 0·5/60 | 3/60 | 0·5/60 | 3/60 |
| 4 | * | * | * | * |
| 6 | 6/60 | 2/60 | 6/36 | 2/60 |
| 7 | 5/60 | 0·5/60 | 6/60 | 0·5/60 |
| 8 | 6/18 | 6/12 | 6/18 | 6/12 |
| 9 | 1·5/60 | 6/36 | 1·5/60 | 6/36 |
| 10 | 6/60 | 6/60 | 6/60 | 6/24 |
| 11 | * | * | * | * |
| 12 | * | * | * | * |
| 13 | 6/60 | 5/60 | 6/24 | 6/18 |
| 14 | 3/60 | 6/60 | 6/60 | 6/36 |
| 15 | * | * | * | * |
| 16 | 1/60 | 6/9 | 1/60 | 6/9 |
| 17 | 6/6† | * | 6/6† | * |
| 18 | 6/36 | 6/18 | 6/18 | 6/12 |
| 19 | 6/6† | 0·5/60 | 6/6† | 0·5/60 |
| 21 | 6/9 | 6/24 | 6/7·5 | 6/12 |
| 22 | ?† | * | ?† | * |
| 23 | 3/60 | 6/60 | 3/60 | 6/60 |
| 24 | 6/60 | 6/36 | 6/60 | 6/36 |
| 25 | 6/36 | 6/60 | 6/36 | 6/60 |
| 26 | 3/60 | 1·5/60 | 3/60 | 1·5/60 |
| 27 | 6/7·5 | 6/7·5 | 6/6 | 6/6 |
| 28 | 6/60 | 6/36 | 6/60 | 6/36 |
| 29 | 6/12 | 6/7·5 | 6/7·5 | 6/6 |
| 30 | 6/12 | 6/18 | 6/12 | 6/12 |
| 31‡ | 6/6 | 6/6† | 6/6 | 6/6† |
| 32 | * | 6/18 | * | 6/12 |
| 33‡ | 6/7·5 | 6/6† | 6/6 | 6/6† |

*Blind eye.
†Eyes which were deemed not to have ONH.
‡Patients with segmental ONH.
?=The visual acuity of this patient could not be subjectively tested.

Considering the axes of astigmatism in the 58 eyes with ONH, in 63% of the eyes with astigmatism the axis (of the positive cylindrical lens) was either vertical or horizontal to within 5°. In 37% the axis was oblique. Seven patients (23%) with bilateral ONH had either a horizontal or vertical axis of astigmatism in one eye and oblique axis in the other eye. In only three patients were the axes of astigmatism opposite to each other in the two eyes (within 5°).

Patients with bilateral ONH and whose visual acuities were known were divided into two groups. The first group comprised patients with visual acuities worse than 6/36 in the better eyes (9 patients), and the second group comprised patients with visual acuities of 6/36 or better in the better eyes (15 patients). The degrees of astigmatism in the better eyes was compared in the two groups (the average degree of astigmatism for the two eyes was taken for a patient when the visual acuities were the same in the two eyes). There was no statistically significant difference in the severity of astigmatism between the first group (mean 1·23 dioptres), and the second group (mean 1·84 doptres) (Welch's test, $p>0{\cdot}1$).

The mean total spherical power in the normal subjects was +2·26, while this was +1·6 for the eyes with ONH in the patient group. However, this trend was not statistically significant (Welch's test, $0{\cdot}1<p<0{\cdot}2$).

The visual acuities could be assessed in 30 of the patients. The unaided visual acuities ranged from no light perception to 6/7·5 (Table II). The unaided visual acuities were 6/6 in the patients with segmental ONH.

## Discussion

The literature on ONH has been reviewed.[16] Forty reported cases of ONH were found in which the refraction had been documented. These were thought to have the same age and sex distribution as the normal population.

The finding in the present paper of a close association of ONH with astigmatism highlights the importance of careful retinoscopy in a child with ONH, in order to optimise visual acuity which may be already substantially impaired. It is therefore recommended that all such children should be refracted at the earliest opportunity.

The mean total spherical power in the patient group was 30% lower than in the normal subjects, suggesting a trend towards myopia. However, this was not found to be statistically significant.

The relationship between ONH and astigmatism is not known, and further investigation by keratometry may shed further light on the association between the two disorders. It is also important that this study is repeated in other such children in order to determine the overall prevalence of astigmatism in ONH.

I would like to thank Dr Anne Alexander for facilitating access to the control subjects, Dr Gordon N Dutton for his assistance in preparing this paper, and Dr Donald Allan for his help with the statistical analysis. I would also like to thank Professor John V Forrester and Dr John Dudgeon for facilitating access to patients under their care.

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MINI REVIEW

# Optic nerve hypoplasia in children

## Abstract

**Optic nerve hypoplasia (ONH) is characterised by a diminished number of optic nerve fibres in the optic nerve(s) and until recently was thought to be rare. It may be associated with a wide range of other congenital abnormalities. Its pathology, clinical features, and the conditions associated with it are reviewed. Neuroendocrine disorders should be actively sought in any infant or child with bilateral ONH. Early recognition of the disorder may in some cases be life saving.**

Optic nerve hypoplasia (ONH) is a non-progressive congenital abnormality of one or both optic nerves associated with a diminished number of axons in the involved nerve(s)[1,2] with normal development of supporting tissues and the retinal vascular system. It gives rise to varying degrees of defective vision ranging from minimal visual impairment (with almost any type of visual field defect) to total blindness. It is now apparent that ONH often occurs in association with several clinically important endocrine and central nervous system (CNS) abnormalities.[3] Ophthalmologists are in a unique position to suspect these conditions so that appropriate investigations and therapy can be initiated. ONH should be suspected in any patient with long-standing non-progressive impairment of vision of indeterminate cause. Segmental ONH[4] and tilted discs in association with ONH[5] have also been described, thus widening the concept of ONH into a larger group of syndromes. However, for the purpose of regarding ONH as a single entity such cases should probably be considered under a different heading.

## Histopathology

Histologically a reduced number of optic nerve fibres can be demonstrated in a smaller than normal optic nerve. The retinal nerve fibre layer is diminished, the ganglion cells are reduced in number, but the outer retinal layers appear normal.[1] The area surrounding the small optic disc may be filled by an overgrowth of retinal pigment epithelium past the normal point of its termination, which gives rise to the 'double ring sign.'[1]

## Pathogenetic mechanisms

The pathogenesis of ONH is not fully understood. The formation of the retina takes place by differentiation of the inner and outer neuroblastic layers. The retinal ganglion cells and nerve fibres develop from the inner neuroblastic layer and appear early, while photoreceptors are the last structure to develop.[6] The ganglion cells differentiate from the inner neuroblastic layer at the 17 mm embryonal stage.[7] The axons grow centripetally and penetrate the mesodermal tissue of the primitive optic disc to form the neural elements of the optic nerve.

Failure of differentiation of the retinal ganglion cell layer between the 12 and 17 mm stages of embryonal development has been suggested as a cause of ONH.[1,7,8] However, this theory implicates selective failure of growth of retinal ganglion cells. This is unlikely, since amacrine and horizontal cells develop from the same precursor neural cells and develop normally in ONH.[1,9,10] Moreover, as ONH is associated with other brain deformities, a pathogenetic mechanism must be proposed which explains the development of such multifocal pathology.

Other mechanisms which have been suggested include stretching of the optic nerve during development of abnormal cerebral hemispheres[11] and, in anencephaly, inadequate target organs which block the development of ascending pathways.[11,12] The funduscopic sign of homonymous hemioptic hypoplasia has been described in three patients with congenital hemiplegia and hemianopia, implicating retrograde axonal degeneration in each optic nerve.[4]

Recent embryological research has shown that overdevelopment of retinal ganglion cells is normally followed by a more than threefold cell death or 'apoptosis,' with consequent axonal degeneration within the optic nerve.[13] It is therefore possible that excessive axonal regression culminates in ONH.

## Aetiology

Little is known about the factors which predispose to ONH. It appears that an insult to the developing optic nerve on or around the 17 mm stage of embryonal development results in optic nerve hypoplasia. A number of teratogenic factors have been suggested. One series of 17[14] and another of four patients[15] have implicated maternal diabetes mellitus as an aetiological factor, but no prospective assessment has yet been carried out.

Postmaturity has also been reported.[16] In one series of 20 cases of ONH nine patients (45%) had been born postmature, but only one had been born premature.

The development of ONH may also be related to young maternal age.[17] In one series of 51 case the mean maternal ages for ONH and a control group were significantly different at 22·1 years and 25·1 years respectively.[18] Young maternal age has also been reported in association with septo-optic dysplasia, with septo-optic-pituitary dysplasia, and with isolated optic nerve hypoplasia.[17,19] It is, however, possible that this association stems from a higher incidence of drug abuse among these young mothers rather than from low maternal age as such.[20]

ONH may also be more common in first born children than later born.[18,21,23] The reason for this is not apparent.

ONH has been reported in 48% of cases of fetal alcohol syndrome,[24] suggesting that alcohol is a major teratogen to the developing optic nerve. In that study a hypoplastic optic disc was defined as a size equal to or less than 2·07 mm,[2] with the funduscopic signs of a double ring with sharply defined margins. However, it could not be ruled out that some mothers might also have used psychopharmaceutic drugs during pregnancy. An admitted history of alcohol abuse was obtained in 12·5% of mothers of children affected by the disorder.[23] Maternal use of anticonvulsants,[25] quinine,[26] lysergic acid diethylamide (LSD),[27] and phencyclidine[28] during pregnancy have been associated with optic nerve hypoplasia.

It is possible that smoking during pregnancy might have a

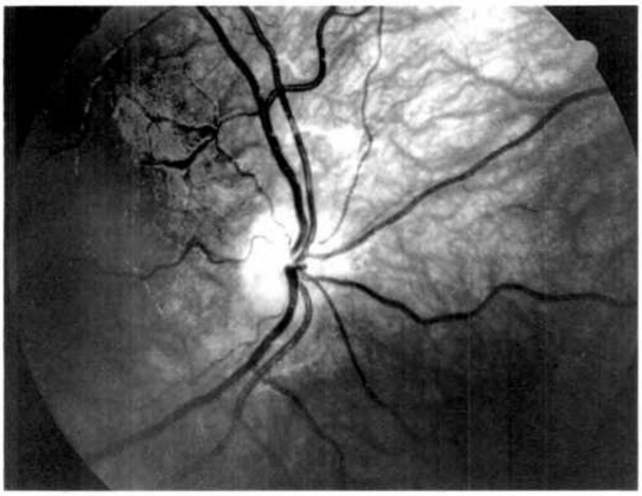

*Figure 1: Appearance of the optic disc in optic nerve hypoplasia.*

similar effect on the developing fetus, but there has been no study which has sought the appropriate data.

An autosomal dominant trait has been implicated in one family with five affected members,[29] but for the other reported cases insufficient data have been available to implicate a specific inheritance pattern.

Cytomegalovirus infection during pregnancy has been implicated as a cause of impaired optic nerve development in four infants.[30]

### Clinical features

Optic nerve hypoplasia may be seen in three situations: (1) as an isolated abnormality in an otherwise normal eye; (2) in grossly malformed eyes; (3) in association with a heterogeneous group of disorders most commonly involving the midline structures of the brain.

The degree of hypoplasia in ONH can vary considerably as can the clinical signs. In severe cases the diagnosis is clearly apparent. The small optic disc(s) and the double ring sign (Fig 1) are the hallmarks of the severe condition. The double ring sign indicates that a small nerve is present within the confines of a wider scleral canal. In less marked cases the diagnosis is reached first by clinical suspicion and the subsequent measurement of the relative and absolute size of the disc (see below). Abnormal visual fields and nerve fibre layer photographs provide additional supportive evidence for the diagnosis.

Bilateral disease has increasingly been reported as more common than unilateral disease.[10 20 23 31] The incidence of ONH in males and females is equal.[21 23 31] Asymmetrical as well as severe unilateral ONH commonly presents with concomitant squint. These cases are often misdiagnosed as primary squint. Trial of occlusion therapy is worthwhile in early childhood, as there may be treatable superimposed amblyopia.[32] Moreover, ONH may leave the papillomacular bundle more or less intact.[33] Bilateral severe cases of ONH usually present with nystagmus or poor vision. A patient with ONH may have normal visual acuity but have visual field defects that pass undetected until later in life. Patients may also present because of the associated neuroendocrine abnormalities.[31]

### Visual acuity

Impairment of visual acuity in ONH is variable. It can thus be difficult to assess the visual potential of a child with ONH on the basis of the appearance of the disc alone.[3 34 35] Cases of ONH with normal visual acuities but with considerable defects in the inferior segments of the visual fields have been reported.[32 33]. As such patients have no difficulties in work or other daily activities, the discovery of visual field defects may lead to the late diagnosis of ONH in patients with normal visual acuity. Such defects can raise the erroneous suspicion of neurological disease and may lead to unnecessary investigation [35 36]

#### PUPILLARY LIGHT REACTIONS

Careful assessment of the pupillary light reflex is very important in suspected cases of ONH, since there is usually some demonstrable degree of afferent pathway defect. This includes cases with normal visual acuity but with extensive field defects. In unilateral or asymmetrical cases the Marcus-Gunn pupil can be elicited.

#### REFRACTION

In 40 eyes reported on in which the refractive state has been recorded the spherical and cylindrical components were distributed as in the general population.[37]

#### OPHTHALMOSCOPIC FINDINGS

The small size of the optic disc may be apparent on funduscopy. However, careful study of fundus photographs is recommended in all cases for which the diagnosis is uncertain, or when the degree of the optic nerve abnormality is in doubt.[31 34 38] A slightly raised and blurred appearance of the optic disc margin characterises the normal appearance.[24] In hypoplastic optic discs there is a diminished number of nerve fibres at the disc border which may account for the sharply defined margins.[39] The commonest change seen round the optic disc is the presence of a circumpapillary halo, the size of which usually corresponds to that of the normal disc.[37] This gives rise to the appearance commonly described as the 'double ring sign.' The halo seen round the disc may be pigmented or non-pigmented and circumferential or partial.[37]

The macula may show a flattening of the normal contours and loss of the foveal light reflex.[40] These changes are due to the relative absence of nerve fibres, the paucity of which can be discerned with red-free light.

The retinal vessels are usually of normal appearance, as the mesodermal elements are not involved. However, retinal vascular tortuosity has been reported in association with ONH.[41]

#### VISUAL FIELDS

Visual field defects are only occasionally described in ONH, mainly because most patients are too young for accurate perimetry. However, in 17 patients with ONH in whom the fields were tested it was shown that the commonest visual

TABLE I *The neurological conditions associated with optic nerve hypoplasia*

| *Condition* | *References* |
|---|---|
| Porencephaly | 10, 64 |
| Cerebral atrophy | 9 |
| Microencephaly | |
| Anencephaly | 79 |
| Hydrocephaly | 18 |
| Hydranencephaly | 1, 18 |
| Perinatal encephalopathy, cerebellar atrophy, cerebral palsy, mental retardation, and cerebral infarcts | 18 |
| Encephaloceles | 10 |
| Colpocephaly | 80 |
| Basal encephalocele | 81 |
| Congenital suprasellar tumours | 53, 82 |
| Occasionally congenital third, fourth and sixth nerve palsies and up-gaze palsy | 83 |
| Behavioural problems | 18 |

field abnormalities comprised bitemporal defects (seven cases) and generalised constriction (six cases).[23] Bitemporal hemianopia in ONH may be a helpful sign to detect the presence of midline defects of the central nervous system (CNS).[11,42]

Other authors have reported another 17 patients with segmental ONH and good visual acuity who were all the offspring of diabetic mothers; most had bilateral inferior altitudinal visual field defects which spared fixation.[14] Several other forms of visual field defects have been reported, including binasal defects, small arcuate defects, and centrocaecal scotomata.[34] The relationship of the pattern of the field defects to the underlying cause or association has not been established.

### COLOUR VISION

Colour vision testing has been performed in one case and was reported as being abnormal.[21] No information was given on the nature of the abnormality. Colour visual function has been mentioned in only one other patient who had bilateral ONH, and it was reported as being normal in both eyes.[43]

### DIFFERENTIATION FROM HYPERMETROPIA

ONH should be differentiated from high hypermetropia, which may give a false impression of hypoplasia. Therefore the refractive state of the eye should always be assessed. The small optic disc may be difficult to diagnose, and clinical judgment is necessary in such cases, since there are no absolute criteria and no readily available techniques for accurate measurement. Ophthalmoscopic diagnosis of optic nerve hypoplasia may be equivocal in hypermetropic patients, in cases of bilateral mild hypoplasia, and in cases of subtle unilateral hypoplasia of the optic disc. In such cases red-free fundus photography with high resolution film can be used to examine the retinal nerve fibre layer for evidence of defects which correspond with the visual field loss.[39] However, many cases of ONH show a uniformly thin nerve fibre layer. This particular type of defect is much more difficult to define with certainty than are focal defects.[44]

Absolute measurement of the size of the optic disc is difficult even in emmetropic eyes, because variation in size can substantially alter the total dioptric power despite no correction being required.[45] An alternative method is to compare the diameter of the optic disc with other measurable parameters in the same eye. But this assumes that the paired parameters bear a constant relationship to each other. The disc-macula: disc diameter ratio as measured from fundus photographs when greater than 3 indicates milder forms of ONH.[46-48]

The size of the disc image in fundus photographs is influenced by the anatomical dimensions of the eye, including the axial length, corneal curvature, and the shape of the fundus,[49] and by refractive errors and optical aberrations. The magnitude of these factors is generally not known for individual eyes. Absolute measurements may be achieved by using interference fringes to produce a scale on the optic disc,[50] but this method requires sophisticated instrumentation and a very co-operative patient.

Franceschetti and Bock[51] measured the disc diameter by means of focal illumination of the fundus with a slit-lamp, using contact lens biomicroscopy with a micrometer scale. Estimation of the size of the optic disc by comparing the slit beam width on the Haag-Streit 900 slit-lamp with the optic disc on contact lens biomicroscopy has also been employed to measure hypoplastic optic discs.[52] These 'measurements' are useful in comparing the diameter of the optic disc relative to the slit-lamp beam or the scale, as their magnification when projected on the optic disc is assumed to be the same as the magnification of the optic disc, which is produced by the optical system of the eye. Comparing the size of the disc with the size of the whole part of the fundus as seen in the standard fundus photograph has also been suggested.[53] Indirect ophthalmoscopic measurement with a scale on the frontal or ocular lens has also been proposed.[54]

Direct measurement of the orbital part of the optic nerve is possible by CT scanning. A-scan ultrasonography[23] and B-scan ultrasonography[55] may also be useful.

### DIFFERENTIATION FROM OPTIC ATROPHY

ONH is sometimes incorrectly diagnosed as optic atrophy.[34] Although glial tissue usually imposes a rather pale colour on the disc in ONH,[56] the disc may be of normal colour. Red-free light ophthalmoscopy can be useful in delineating the area of the optic disc.

It has been suggested that non-progressive optic atrophy acquired any time before full development of the eye and the visual pathway, can produce a small atrophic optic disc which resembles that of ONH.[39]

In an infant, examination with sedation or general anaesthesia, including fundus photography, may be required to differentiate ONH from optic atrophy. This differentiation is important in order to plan the investigation of the patient appropriately and also to provide adequate background data for counselling the parents.

### RADIOLOGY OF THE OPTIC CANALS

Reduction in the size of the optic canals may be seen on *x*-ray.[57] The technique of axial tomography of the optic canals has been found more useful in this regard than plain foraminal views.[55] However, there is a significant range of normal diameters of the optic canal on each side which may result in a 20% difference in size.[38] There is no good correlation between ONH and the degree of diminution of the diameter of the optic canal as seen with optic foraminal projection.[21]

### ELECTROPHYSIOLOGICAL FINDINGS

The electroretinogram and electro-oculogram in isolated ONH are normal, but the amplitude of the visually evoked response (VER) is commonly reduced. However, it appears that the VER is useful only as a correlate with the clinical assessment of vision.[18,58,59] Severe bilateral cases of ONH which present in early infancy may need to be differentiated from conditions such as achromatopsia and Leber's amaurosis. In these cases the demonstration of a normal ERG response can be of critical diagnostic importance.

TABLE II *Ocular and systemic conditions associated with optic nerve hypoplasia*

| *Condition* | *References* |
|---|---|
| Aniridia | 84 |
| Albinism | 74, 85 |
| High myopia | 10 |
| Chorioretinal and optic nerve head coloboma | 56 |
| Aicardi syndrome | 86, 87 |
| Potter's syndrome | 88 |
| Microphthalmos | 83 |
| Klippel-Trenaunay-Weber syndrome | 89 |
| Goldenhar-Gorlin syndrome | 90 |
| Duane's retraction syndrome | 91 |
| Hemifacial atrophy | 38 |
| Meckel syndrome | 92 |
| Blepharophimosis | 93 |
| Chondrodysplasia punctata | 94, 95 |
| Osteogenesis imperfecta | 96 |
| Deletion of the long arm of chromosome 13 (13q−) | 97 |
| Triosomy 18 'Edward's syndrome' | 98 |
| The syndrome of naevus sebaceus of Jadassohn | 99 |
| Midline facial defects including harelip, cleft palate, and hypertelorism | 100 |

## Associations of ONH

### SEPTO-OPTIC DYSPLASIA

ONH is seen in 25% of cases of agenesis of the septum pellucidum.[60] Conversely, 27% of patients with ONH had partial or complete absence of the septum pellucidum.[18] This condition is known as septo-optic dysplasia. The neurological features of this condition are mental retardation, spasticity, abnormalities of taste, and impaired smell.[61] However, some patients have only mild deficits, with normal intelligence.[61] Ablation of the septum pellucidum in animals impairs their ability to learn tasks requiring spatial orientation.[62] A spatial learning disorder in a 13-year-old girl with severe ONH and absence of the septum pellucidum has been reported.[63] It may therefore be useful to look for this lesion in such children so that they may get the best education.

### OTHER NEUROLOGICAL ASSOCIATIONS

ONH is associated with a large number of other neurological disorders (Table I).

### ENDOCRINOLOGICAL ASSOCIATIONS

Pituitary dysfunction arising as a consequence of hypothalamic maldevelopment may accompany septo-optic dysplasia.[18 61 65 67] Moreover, ONH with a normal septum pellucidum may also be associated with hypopituitarism,[68] the degree of which may vary between subclinical disorder and panhypopituitarism. It is clearly important to establish the diagnosis in infancy so that optimal replacement therapy can be given.[61 68] Since the coincidence of pituitary hypofunction and optic nerve hypoplasia was first reported in 1970,[69] the true incidence of hypopituitarism with ONH has not been determined in a large series of patients. Furthermore, unlike patients with idiopathic hypopituitarism, who commonly show delayed growth beginning at 6 to 15 months of age, children with septo-optic dysplasia and a deficiency of growth hormone frequently have normal growth until their third or fourth year of life.[20 64] Diabetes insipidus has also been reported in association with bilateral ONH and in association with septo-optic dysplasia.[70] Necropsy on one patient who had bilateral severe ONH, hypopituitarism, and diabetes insipidus showed the cells of the supraoptic and paraventricular nuclei to be abnormally small and few in number.[22] Pituitary dysfunction may also show as prolonged neonatal hyperbilirubinaemia, hypotonia, infantile hypoglycaemia without hyperinsulinaemia, hypothyroidism, and growth retardation.[22 64 71] Pituitary dysfunction can complicate general anaesthesia, especially if it has not been recognised preoperatively.[72] In one series of 93 cases of children with ONH hypothyroidism was the most frequent endocrine disturbance.[10] This was an unexpected finding, in view of the frequently emphasised principal association of ONH and growth hormone deficiency.

### NEURORADIOLOGICAL FINDINGS IN SEPTO-OPTIC DYSPLASIA

The anatomical defects of septo-optic dysplasia may be subtle, and an apparently normal septum pellucidum on CT does not invalidate a clinical diagnosis of a mild form of septo-optic dysplasia.[73] For cases of bilateral ONH a CT scan is usually indicated to exclude midline or other cerebral structural abnormalities.[74]. In particular it has been recommended that children with bilateral ONH, nystagmus, and poor vision should undergo a thorough neuroradiographic and endocrine examination.[20] It has been shown that CT accurately delineates the altered anatomy of septo-optic dysplasia.[75] Enlargement of the pituitary stalk and infundibulum may be seen when septo-optic dysplasia is associated with diabetes insipidus.[75] Dilated ventricles were also noted.[66 76] Neuroradiographic abnormalities were reported in 39% of 41 children who had bilateral ONH, poor vision, and nystagmus.[20] These abnormalities included absence of the septum pellucidum, absence of the corpus callosum, encephaloceles, porencephaly, and hemispheric atrophy.

Real time cranial ultrasound can be used in infants to image cerebral structures.[77 78] Magnetic resonance imaging (MRI) has been used in the newborn to investigate intracranial structure and pathology. However, the role for MRI in cranial imaging of infants has not been clearly defined.[77]

### OTHER OCULAR AND SYSTEMIC ASSOCIATIONS

A large number of other systemic and ocular associations with ONH have been reported (Table II).

## Conclusion

ONH should be sought in any child with poor vision or in patients labelled as having amblyopia resistant to occlusion. All children with ONH, particularly those with severe visual loss, and all bilateral cases with impaired vision, should have a careful clinical examination including a CT scan. The general physical examination of the child with special reference to height and weight may indicate the need for investigation of pituitary function and should be performed on all children with an abnormal CT appearance. The frequent association of CNS anomalies and endocrine problems with ONH is an important piece of information which the attendant ophthalmologist must convey to the paediatrician and the family practitioner, with a view to arranging appropriate and early treatment.

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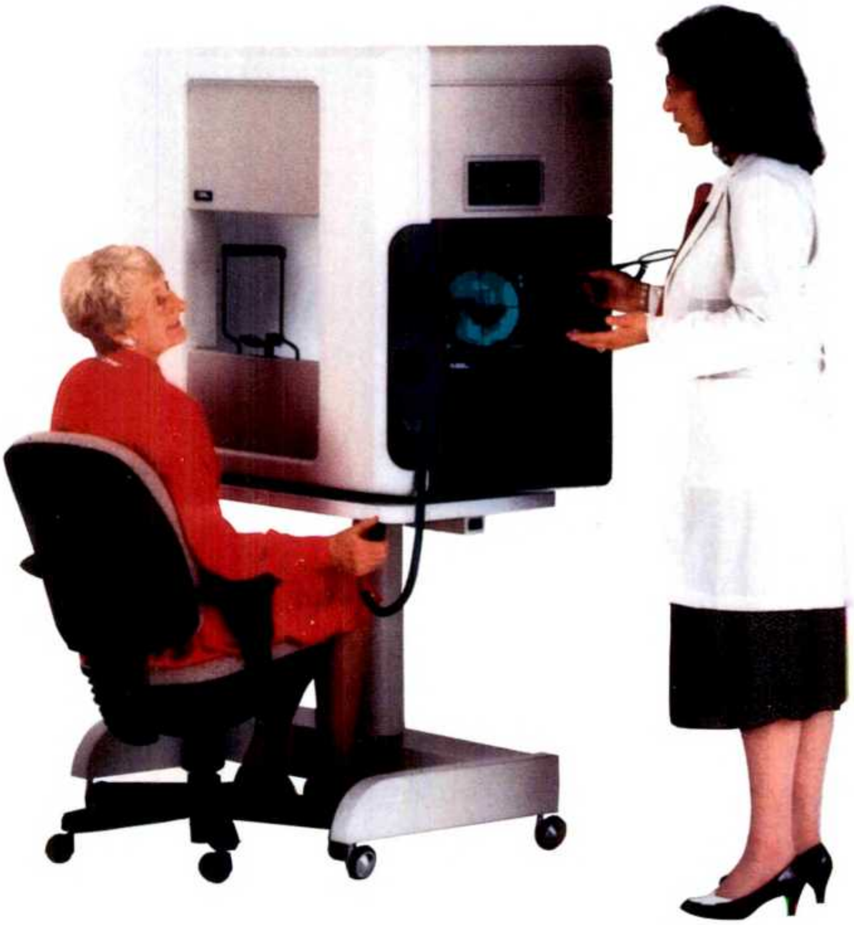

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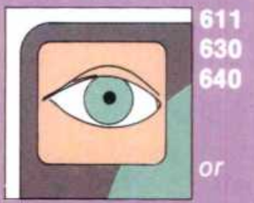

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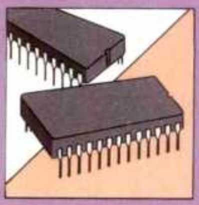

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CASE REPORTS

# Colour Doppler imaging in the demonstration of an orbital varix

Wolfgang E Lieb, Daniel A Merton, Jerry A Shields, Steven M Cohen, Donald D Mitchell, Barry B Goldberg

**Abstract**

**Colour Doppler imaging (CDI) is a recent development in ultrasonography. It allows simultaneous two-dimensional structural imaging and Doppler evaluation of blood flow. Quantitative information on flow velocity is obtained by pulsed Doppler spectral analysis, the colour information being used to choose the vessel of interest. Using this technique the authors examined a patient with an orbital varix previously diagnosed by clinical findings and computed tomography. Dynamic evaluation with real-time direct imaging of flow facilitated the diagnosis of this orbital disorder without the need for any contrast material. This technique may prove to be a useful adjunct to computed tomography for the evaluation of suspected vascular lesions of the orbit.**

Primary orbital varices are relatively uncommon congenital vascular anomalies.[1-5] The orbital varix is defined as a pathological enlargement of one or several venous channels. Orbital varices are usually diagnosed in the first three decades of life,[6] have no sex predilection, and are generally unilateral, though a bilateral case has been reported.[7]

Affected patients typically present with intermittent unilateral proptosis that can be accentuated by straining, coughing, the Valsalva manoeuvre, and positional increase of venous pressure in the head and neck region.[8] Rarely these patients present with severe pain, sudden orbital haemorrhage, and visual loss, necessitating surgical excision of the varix.[9-13]

In addition to a physical examination the diagnostic tests for orbital varices include orbital computed tomography with a Valsalva manoeuvre[6 14-16] and orbital venography.[17-19] We examined a patient with a large orbital varix by means of colour Doppler imaging (CDI). CDI is a relatively recent advance in diagnostic imaging that is used to study vascular disorders throughout the body and represents an alternative to invasive vascular studies such as venography and arteriography.[20-22] Guthoff *et al.* have recently applied Duplex scanning and CDI to the eye, and they demonstrated the usefulness of this technique to depict blood flow in intraocular tumours.[23] The same group measured central retinal artery and central retinal vein blood flow by duplex sonography.[24] While Duplex scanning without colour information can detect flow in larger vessels under two-dimensional B-scan control, in the orbit the diameters of most vessels are below the B-scan resolution. Therefore flow information cannot be obtained accurately and selectively in these small vessels. Recently CDI was used to detect and quantify muscle movements by measuring frequency shift during voluntary saccades.[25]

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## Patient and methods

The colour Doppler unit used for our study (QAD 1, Quantum Medical Systems, Inc, Issaquah, Washington) has 5·0 and 7·5 MHz linear phased transducers. The estimated in-situ peak temporal average (SPTA) intensities in the colour imaging mode (provided by Quantum Medical Systems) are 2–3 mW/cm$^2$ for the 7·5 MHz transducer. When spectral analysis is performed the SPTA intensity is approximately 25 mW/cm$^2$. In the spectrum analysis mode the SPTA intensity exceeds slightly the limits of 17 mW/cm$^2$ currently suggested by the Food and Drug Administration guidelines, so that spectrum analysis with pulsed Doppler was performed only for a short time, approximately 30 seconds.

Depending on the direction of flow with respect to the transducer, the flow is displayed in either red or blue. The colours can be arbitrarily assigned, but by convention, and in this study, flow towards the transducer is depicted as red and away from the transducer as blue. When the eye and orbit are examined through the eyelids, the ultrasound beam is almost parallel to the orbital and ocular vessels; thus most arterial flow is depicted in red. Arteries can usually be distinguished from veins by noting the pulsatility of the former. Pulsed Doppler spectral analysis also helps to distinguish between pulsatile arterial and non-pulsatile venous flow and allows quantification of data. When the ultrasound beam is at an angle of 90° to a vascular structure, or if a vessel contains only stagnant blood, no Doppler flow information is obtained and the structure is shown in grey scale display only.

Our patient was a 38-year-old woman who had positional proptosis of the left eye and classic findings of an orbital varix on computed tomography.[5 26] A contact gel (Aquasonics) was

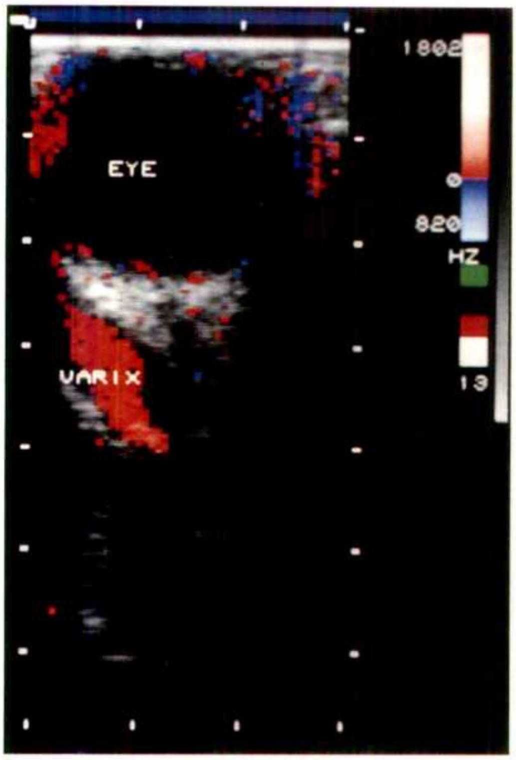

*Figure 1: Vertical scan toward the temporal orbit. The patient starts to perform a Valsalva manoeuvre. Deep in the orbit there is a well circumscribed structure with flow towards the ultrasound probe, depicted in red.*

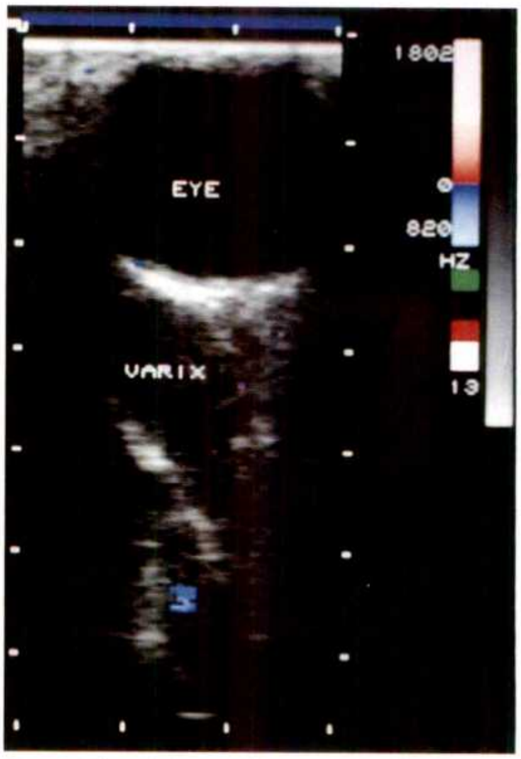

*Figure 3: The varix is maximally expanded. Diffuse low level echoes fill the lumen. No flow information is depicted, since the blood at the height of the Valsalva manoeuvre is stagnant.*

applied to the closed eyelids, and horizontal and vertical scans through the eye and orbit were performed in a standard fashion.

## Results

To allow better orientation the V-shaped optic nerve shadow was displayed first. Within this shadow the pulsating central retinal artery and the accompanying central retinal vein were identified. Deeper into the orbit the main branch of the ophthalmic artery was also seen. No abnormalities in the echographic pattern of the eye and orbit were noted. On request the patient performed a Valsalva manoeuvre. In the superotemporal orbit there was a slowly expanding vascular space with marked flow toward the transducer and therefore demonstrated in red (Fig 1). On relaxation the size of the lesion slowly decreased, with flow away from the transducer, depicted in blue (Fig 2). During the extension of the varix displacement of the optic nerve was noted. On maximal dilation no colour information was obtained, indicating the cessation of blood flow (Fig 3).

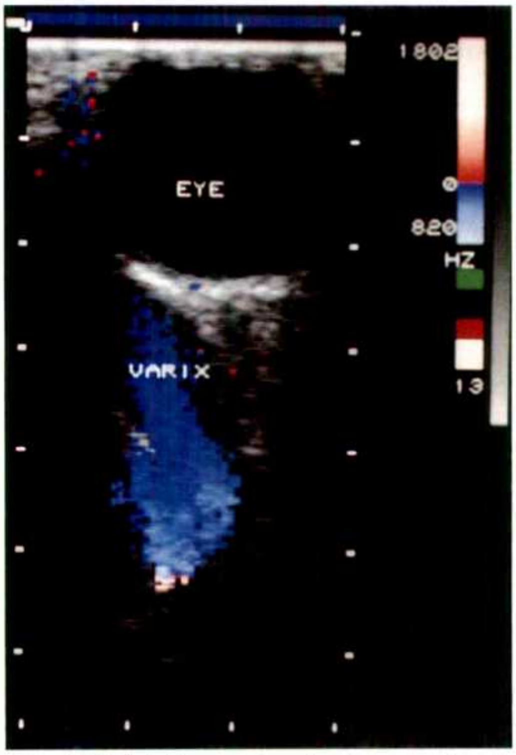

*Figure 2: With the decrease in intrathoracic pressure the varix empties. Flow is directed towards the orbital apex away from the ultrasound probe and therefore depicted in blue.*

Pulsed Doppler spectral analysis of the varix demonstrated that influx and efflux were non-pulsatile and continuous – characteristic for venous flow (Fig 4). When the vein collapsed on expiration, flow was seen to increase in velocity and was directed away from the ultrasound probe (Fig 5). Normal-appearing extraocular muscles were seen.

## Discussion

Colour Doppler imaging (CDI) allows colour encoded flow data of a vascular structure to be displayed simultaneously on a conventional real-time grey scale B-mode image. This requires a highly sophisticated processing of the returning echoes. In conventional B-mode imaging the amplitude of the returning echoes is converted into a two-dimensional image, and frequency shifts of moving acoustic reflectors are ignored. With CDI the ultrasound signal is detected and analysed in real time for changes in echo ampli-

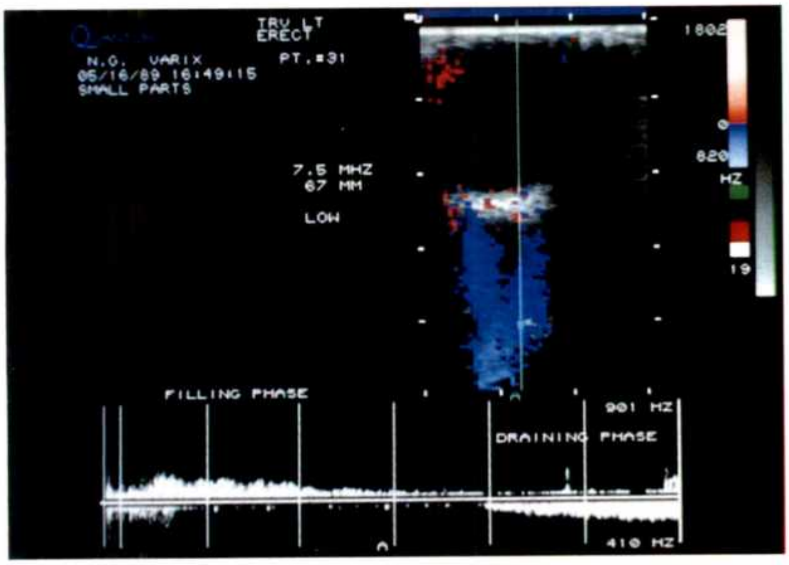

*Figure 4: Spectral analysis of the varix demonstrates the filling phase (above baseline) and the drainage phase (below baseline). Both show continuous flow patterns without pulsations characteristic for venous flow.*

tude, frequency, and phase shift. The results are displayed as a composite image of two-dimensional grey scale with superimposed colour encoded flow information.[21 22 27] Recent articles[28 29] have stressed the importance in the examination of anatomical and functional disorders in the cerebrovascular system in newborns. As it is often difficult to differentiate certain vascular lesions, such as capillary haemangiomas, cavernous haemangiomas, orbital varices, and arteriovenous malformations[3 5] from solitary non-vascular epithelial or lymphoid lesions, CDI may prove to be particularly useful.

Although intermittent pulsating exophthalmos is rather characteristic and in many cases diagnostic of an orbital varix, imaging of the varix is mandatory for confirming the diagnosis and to demonstrate the extent of the lesion.

In the past orbital venography was traditionally used to diagnose and demonstrate the location of orbital varices.[30 31] However, severe adverse reactions have been reported with this technique.[32] In many cases plain computed tomography (CT), contrast enhanced computed tomography, and magnetic resonance imaging (MRI) fail to diagnose an orbital varix unless a Valsalva manoeuvre is performed during the examination.[26]

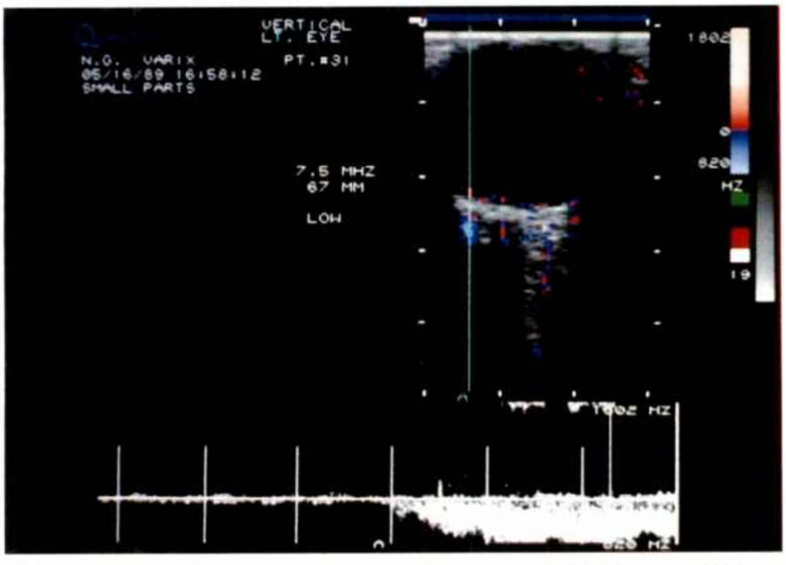

*Figure 5: The varix is almost collapsed. In the residual lumen a very high frequency shift is detectable.*

Since most cases of uncomplicated varices are not treated and surgical management is advocated only when complications occur, we believe this new ultrasonic technique is preferable to standard A- and/or B-scan ultrasonography. Although these conventional ultrasound techniques have been shown to depict an orbital varix they do not directly demonstrate the blood flow.[33-35] CDI appears to be a simple procedure for definitive diagnosis of an orbital varix. If, however, surgical intervention is being considered, further studies as axial and coronal computed tomography with a Valsalva manoeuvre and perhaps an orbital venogram should be employed to assist in surgical planning.

We believe that colour Doppler imaging carries great promise for the study of other ocular and orbital vascular diseases. Further studies in this field are under way in our departments to explore the potentials of this new technique.

Wolfgang E Lieb is an Ocular Oncology Fellow on the Oncology Service of Wills Eye hospital sponsored by the DFG, West Germany.

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*British Journal of Ophthalmology*, 1990, 74, 309–310

# Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm

P Corridan, S Nightingale, N Mashoudi, A C Williams

## Abstract

**Botulinum toxin inhibits acetylcholine release and therefore could cause mydriasis. We report a case of acute angle-closure glaucoma which occurred shortly after a series of injections of botulinum toxin round the eyelids for blepharospasm.**

Botulinum toxin as a therapeutic agent was introduced by Scott in 1980[1] for the treatment of squint, and more recently idiopathic blepharospasm has been successfully managed by injection of botulinum toxin into the orbicularis muscle to produce mild paresis. Many hundreds of patients with blepharospasm have been treated without any sight threatening side effects.[2] We report a case of acute angle-closure glaucoma occurring shortly after botulinum toxin injection for blepharospasm.

## Case report

An 83-year-old woman with a long history of idiopathic blepharospasm was started on botulinum toxin therapy. She had a past history of dry eyes, bilateral macular degeneration, and bilateral levator resections for ptosis. She received a series of injections by a conventional technique.

### TECHNIQUE

0·05 mg of freeze-dried botulinum toxin – haemagglutin complex (0·008 mg neurotoxin) was reconstituted with 1 ml of sterile saline and then diluted in a further 9 ml of saline.[3] A 0·5 ml syringe with a 0·36 mm×12·7 mm needle was used. Four injections of 0·1 ml or 0·15 ml were given subcutaneously round each eye, two immediately above each eyebrow and two a similar distance below the eye.

Initially she received two 0·15 ml injections above each eye and two 0·1 ml injections below each eye, with good relief from blepharospasm and no side effects. Thirteen weeks later blepharospasm had recurred on the right but not on the left. She received two injections of 0·1 ml of toxin above each eye.

Three hours later she developed an ache about her left eye, and within six hours this had become severe and was associated with blurred vision in the left eye, nausea, and vomiting. Despite her severe symptoms she did not seek medical help for her eye condition for a further three days. On examination at the eye casualty department the visual acuity was 6/36 in her right eye and perception of light in her left eye. The conjunctiva and episclera of her left eye were inflamed and the cornea was oedematous.

The intraocular pressures were 60 mmHg in her left eye and 18 mmHg in her right. The left pupil was semidilated and the iris was atrophic. Gonioscopy in the left eye was not possible owing to marked corneal oedema, but the drainage angle in the right eye was very narrow. A diagnosis of left angle-closure glaucoma was made.

She was treated with acetazolamide 500 mg intravenously immediately and also with topical pilocarpine to both eyes and topical prednisolone to the left eye. Two hours later the intraocular pressure had fallen to 36 mmHg in the left eye, and her pain was less severe. Over the next four days the left intraocular pressure remained under control at 28 mmHg, though the cornea was oedematous. Bilateral laser iridotomies were performed with a neodymium-yttrium-aluminium-garnet laser. Three months later the corneal oedema resolved, but, as the intraocular pressure remained high, trabeculectomy was performed. A month later the left visual acuity was counting fingers, which was approximately the same as the patient had before acute glaucoma developed.

## Discussion

Botulinum neurotoxins act primarily at peripheral cholinergic synapses, where they inhibit the release of acetylcholine.[4] They are used clinically for their action on the skeletal muscle neuromuscular junction, causing transient muscle paresis. However, botulinum toxins also inhibit acetylcholine release at sympathetic ganglia and at the preganglionic and postganglionic nerve terminals of the parasympathetic nervous system. People systemically poisoned with botulinum toxins characteristically have mid-dilated fixed pupils due to paralysis of the sympathetic and parasympathetic innervation to the iris.[5] Botulinum toxins could therefore cause pupil dilatation by uptake into the parasympathetic neurones at the level of the ciliary ganglion or at the parasympathetic neuromuscular junctions in the sphincter pupillae of the iris. It has been shown in animal studies that botulinum toxin injected intracamerally[6] or near the ciliary ganglion[7] causes mydriasis. We propose that in this patient's eye, which was predisposed to angle closure, acute glaucoma was precipitated by mydriasis caused by botulinum toxin injection around the eye.

Elston[3] reported a series of 243 patients treated with botulinum toxin for involuntary facial movements, mainly blepharospasm. Some developed diplopia, presumably due to diffusion of the toxin from the orbicularis muscle into the oculomotor muscles. Three patients complained of blurred vision, and it is possible that they had

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ciliary muscle paresis with or without pupil dilatation as a result of botulinum toxin injection.

Scott *et al* reported a fourfold increase in the incidence of ptosis in patients who, like our patient, had had previous lid surgery.[8] Diffusion of the toxin into adjacent tissues may be greater in this group.

Angle-closure glaucoma did not occur until the second series of injections in our patient. Similarly, cases of mydriatic glaucoma seen in outpatients have often had their pupils dilated uneventfully on more than one occasion before developing angle closure.[9] (Smith RJH, personal communication.) The symptoms of angle closure in our patient developed only six hours after the injection. Usually the toxin has its maximum effect on the levator on the third postinjection day,[10] when this diagnosis of glaucoma was confirmed. Moreover, the toxin appears to exert an effect more rapidly on the pupils than on skeletal muscle, as in botulism, where blurred vision normally precedes skeletal muscle paralysis.[5]

This is the first reported case of acute angle-closure glaucoma following a therapeutic injection of botulinum toxin. We recommend gonioscopy to assess the potential for angle closure in all adults prior to treatment with botulinum toxin for blepharospasm, and particularly in those who have had previous eyelid surgery. Patients should be warned of this side effect and advised to report symptoms of early acute glaucoma immediately. Those who are shown to be at risk could have prophylactic YAG laser iridotomies.

We thank Miss E M Eagling for permission to report this case and Mr M J Roper-Hall for his help and advice.

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*British Journal of Ophthalmology*, 1990, **74**, 311–312

# Retinoblastoma metastatic to the contralateral orbit

Kanwar Mohan, Amod Gupta, J S Saini, Subhadra Jalali, Kusum Joshi

**Abstract**

**In a 9-month-old girl a subperiosteal metastasis of the maxillary bone developed in the contralateral orbit about one year after enucleation of a poorly differentiated retinoblastoma.**

Studies of necropsy cases of retinoblastoma have shown that about 94–100% of patients have some form of intracranial metastasis and 53% have involvement of distant bones.[1-3] The involvement of orbital bones is by direct spread from the recurrent tumour in the affected orbit, though some authors have considered ipsilateral orbital involvement to be orbital metastases.[1-3] To our knowledge there is no report of retinoblastoma metastasising to the bones of the contralateral orbit. We report an unusual case of unilateral retinoblastoma in which the patient developed subperiosteal metastasis in the contralateral maxillary bone.

## Case history

A 9-month-old girl had had a white pupillary reflex in her right eye since the age of 3 months. Her right eye did not fix light. The anterior segment in this eye appeared normal. On ophthalmoscopy a large greyish-white endophytic mass with prominent feeder vessels was seen in the temporal half of the retina. The intraocular pressure in this eye was normal. Her left eye was normal. A clinical diagnosis of retinoblastoma in the right eye was made and enucleation was advised.

One week later, the child developed orbital inflammation, with swelling of lids, conjunctival chemosis, proptosis, and restricted motility of the right eye. She was afebrile. She responded well to oral anti-inflammatory drugs but was lost to follow up.

When she was seen again 16 months later the anterior segment in her right eye showed signs of healed iritis but no appreciable difference in the morphology of the retinal mass. The intraocular pressure was low, and there were no signs of orbital involvement. Her left eye and orbit were normal. Systemic examination did not reveal any signs of distant metastases. The right eye was enucleated and 800 rads of external radiation were delivered to the orbit. Histopathological examination of the enucleated eye showed poorly differentiated retinoblastoma with extensive necrosis (Fig 1). The iris and ciliary body were necrotic, with focal invasion of the choroid. The optic nerve was free of the tumour.

Eleven months after enucleation of the right eye she developed fullness in the lateral part of the left lower eyelid (Fig 2). The left eyeball was normal but displaced upwards. Eyeball movements were normal. There were no signs of tumour recurrence in the right orbit or of intracranial or distant metastases. A fine needle aspiration biopsy from the mass was consistent with metastatic retinoblastoma. The orbital mass was treated with 800 rads of external radiation and oral cyclophosphamide, but showed no response. On surgical exploration the mass was found to be subperiosteal. A wedge biopsy showed a histopathological picture identical to that of the primary tumour. Two weeks later the

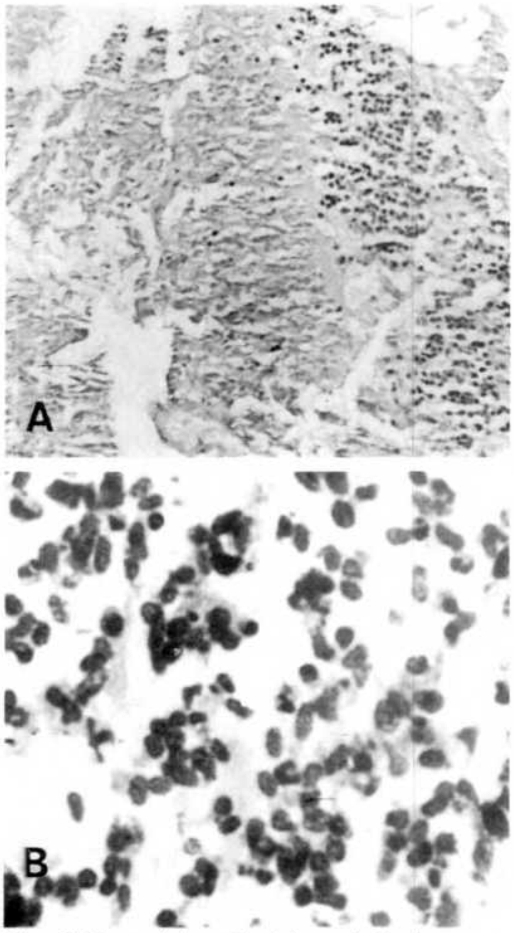

*Figure 1: Histopathology of the right eye. A: Poorly differentiated retinoblastoma with extensive necrosis. (H and E, ×125.) B: Small oval cells with hyperchromatic nuclei and occasional mitoses. (H and E, ×400.)*

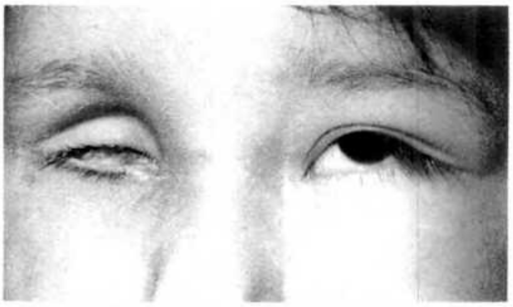

*Figure 2: Fullness of the outer part of the left lower eyelid 11 months after enucleation of the right eye for retinoblastoma. Note slight upward displacement of the left eyeball.*

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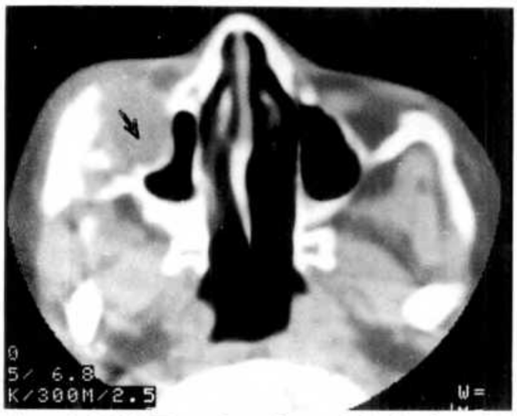

*Figure 3: Axial CT scan shows the mass indenting the roof of the left maxillary sinus (arrow) but without invasion.*

mass increased rapidly and an axial CT scan revealed a soft tissue mass in the anterolateral part of the left lower orbit, with mass impression over the maxillary sinus without actual invasion of the sinus (Fig 3). Treatment with 1800 rads of external radiation led to an initial regression, but within six weeks the tumour invaded the left maxillary sinus and infratemporal fossa. The child died one year after the first appearance of the metastasis.

## Discussion

The distant bones most commonly affected by retinoblastoma metastasis are the ribs and the vertebrae, these being the most active in the haemopoietic system, especially in children.[1] Metastasis to the contralateral orbit in our patient is unique. (Shields J A, personal communication). The metastasis was subperiosteal initially, but later the underlying bone was eroded and the tumour grew into the maxillary antrum. Most of the cases with metastases to the distant bones have involvement of the skull bones as well as the viscera.[3] Involvement of these structures cannot be entirely ruled out in our patient, since laboratory investigations often fail to detect metastases.[3] A non-ocular tumour was ruled out by an identical histological appearance in our patient[4] (Shields J A, personal communication). The average time lag between initial diagnosis of retinoblastoma and the first signs and symptoms of metastasis varies from 5·5 months to 2·1 years.[1-3] In our patient the time interval was 2·3 years.

Patients with tumour recurrence in the orbit are more likely to have distant metastases.[1] Our patient did not show ipsilateral orbital recurrence at any stage of the disease. Choroidal invasion and a poorly differentiated histological type were the only apparent risk factors.[1 5-8] We believe that 16 months delay in enucleation perhaps allowed dissemination of the tumour cells. Once metastases appear, the average survival time is 3·5 to 5·8 months[2 3] (Shields J A, personal communication). Early diagnosis and prompt treatment are of prime importance in reducing the mortality from retinoblastoma.

We are grateful to the staff of the Armed Forces Institute of Pathology, Washington, DC, For histopathological examination of the biopsy from the left orbital mass.

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# Accelerated ocular neovascularisation in diabetics following posterior chamber lens implantation

P Prasad, P H Setna, J A Dunne

## Abstract

**Two well controlled non-insulin dependent diabetics with background retinopathy underwent endocapsular lens extraction with in-the-bag posterior chamber implantation. In the postoperative period rubeosis iridis set in abruptly. The fellow eyes showed no progression of retinopathy and the diabetic status showed no deterioration. The cause of neovascularisation and the role of intra- versus extracapsular extraction with implantation are discussed.**

The effect of cataract extraction on diabetic retinopathy has been regularly reviewed. There is a relatively high incidence of rubeosis iridis after intracapsular extraction (ICCE), particularly with pre-existing proliferative retinopathy.[1] Until recently uncomplicated extracapsular extraction (ECCE) was thought to reduce this risk.[2] Now, ECCE, especially with vitreous loss, is being recognised as leading to progression of non-proliferative retinopathy.[3 4] We report two cases where rubeosis iridis presented abruptly following endocapsular lens extractions with posterior chamber lens implants (PCIOLI) in non-insulin dependent diabetics, with pre-existent background retinopathy.

## Case reports

### CASE 1

A 68-year-old man recently detected non-insulin dependent diabetes was seen in October 1988. He had suffered a cerebrovascular accident three months earlier and was on naftidrofuryl oxalate (Praxilene). The visual acuity was 6/12 in each eye, with bilateral cataracts. Fluorescein angiograms revealed focal leaks at the posterior pole, with no evidence of neovascularisation at the optic disc (NVD). The quality of the films were poor owing to the cataract. In order to facilitate laser photocoagulation, he underwent an uncomplicated endocapsular lens extraction with in-the-bag PCIOLI in the right eye on 27 January 1989. Postoperatively the visual acuity was 6/9 with a pinhole, the intraocular pressure (IOP) was 12 mmHg, and there was no evidence of rubeosis iridis. In March 1989, focal laser photocoagulation was carried out to both posterior poles, treating areas of intraretinal microangiopathy. In May, approximately 14 weeks after the operation, he returned with acute pain and sudden loss of vision in his right eye. The visual acuity was hand movements only, the eye was congested with heavy flare and cells in the anterior chamber. The IOP was 38 mmHg. He was admitted and treatment begun with prednisolone 30 mg orally, dexamethasone eye drops hourly, acetazolamide tablets 250 mg four times a day, and timolol eye drops 0·5% twice daily. Over the next fortnight the eye quietened, frank rubeosis was noted, and gonioscopy revealed a neovascular membrane in the angle. Both systemic and topical steroids were tapered. At his next visit in July 1989 the visual acuity was perception of light only and the IOP was 42 mmHg. The fundus view was not adequate to allow panretinal laser ablation. The left eye retained a visual acuity of 6/12 with no progression in the retinopathy. Throughout this period, the blood sugar was controlled on diet alone, except briefly when he was on systemic steroids at his second admission.

### CASE 2

A 71-year-old man presented in January 1987 with a visual acuity of 6/12 in the right eye and 6/24 in the left. Bilateral posterior subcapsular cataracts were noted. The fundi showed simple background retinopathy with few microaneurysms at the posterior pole. Four months earlier diabetes had been diagnosed and treatment started with glibenclamide 5 mg twice a day. By March 1988 the cataracts had advanced, and the visual acuity had reduced to 6/36 and counting fingers respectively. An endocapsular lens extraction of the left eye was performed on 23 March 1988. A small rent occurred in the central posterior capsule, but this did not hinder satisfactory in-the-bag PCIOLI. On the first postoperative day the visual acuity was 6/9, the IOP was 10 mmHg, and no rubeosis iridis was seen. When he was examined again in May, there was a progression of the background retinopathy in the left eye with dot haemorrhages at the posterior pole. Three months later (five months postoperatively) he presented with a red eye and sudden blurring of vision in the operated eye. The visual acuity was down to 6/12, frank rubeosis iridis and new vessels at the disc were present. The IOP was 46 mmHg. Treatment was instituted with acetazolamide tablets 250 mg four times a day and timolol eye drops 0·25% twice daily. Panretinal laser photocoagulation was undertaken in two sessions, leading to partial regression of the NVD. Despite treatment the visual acuity subsequently deteriorated to 6/60; the IOP was 58 mmHg, and rubeosis iridis remained. The right eye has shown no progression of the retinopathy whatsoever. His blood sugar has remained under control all along.

## Discussion

Neovascularisation of the anterior segment is

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popularly believed to result from diffusion of angiogenic factors produced either by severely ischaemic retina[5] or by increased capillary leakage with release of vasoformative factors, including prostaglandins.[6] It is easier to visualise the latter as occurring after intraocular surgery, when blood-ocular barriers can break down. Does this explain the progression of diabetic retinopathy to rubeosis iridis following lens extractions? The systemic blood sugar control and the status of the fellow eye remained unchanged in both our cases. This further strengthens the possibility of local surgical trauma leading to accelerated neovascularisation.

The next question is one of the relative risk of ICCE versus ECCE. Aiello *et al*[1] noted a higher risk of neovascular glaucoma and rubeosis iridis in patients undergoing ICCE with pre-existing proliferative retinopathy. Experimentally, bovine lens extracts were found to inhibit endothelial cell proliferation.[7] This led to the belief that leaving the posterior capsule intact would diminish the incidence of rubeosis iridis. Two series support this postulate. In 216 eyes Poliner and others[2] found neovascular glaucoma only in ICCE and ECCE with primary capsulotomy; none occurred in ECCE without capsulotomies. Similarly, Jaffe and Burton[3] reported eight cases with progression of pre-existing non-proliferative retinopathy. Of seven cases with ECCE rubeosis occurred in only one eye, which was complicated by vitreous loss. By contrast, Pavese and Insler[4] and now our case 1 have shown rubeosis iridis despite uncomplicated extra/endo capsular lens extractions. The role of the intact posterior capsule as a mechanical/biochemical barrier to rubeosis iridis seems less certain now.

Interestingly, Pavese and Insler[4] reported no progression of retinopathy in the fellow eye of one of the patients when ECCE was carried out subsequently with no PCIOLI. Are there some patients in whom a PCIOLI, despite being in the bag, negates the protective role of the intact posterior capsule? Could the physical presence of a PCIOL in the bag be mechanically blocking the 'angiogenesis inhibitor' from the lens tissue?

If more cases of ECCE and PCIOLI with pre-existing backgound retinopathy are reported with progression to rubeosis iridis, then perhaps routine postoperative panretinal laser ablation will become necessary. This is all the more important as we have shown the clinical picture rapidly change to neovascularisation from one visit to the next. The visual gain following surgery is dramatically and permanently impaired. For the moment we can only suggest regular review at shorter intervals after PCIOLI in diabetics even with simple background retinopathy.

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# Tuberculosis of the conjunctiva occurring in association with a neighbouring lupus vulgaris lesion

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### Abstract

**A case of tuberculosis of the conjunctiva in association with a neighbouring lupus vulgaris lesion is reported. Both lesions resolved within one month of starting antituberculous therapy. Tuberculosis of the conjunctiva is nowadays a rare condition. It should be considered in the differential diagnosis of any unusual chronic conjunctivitis, particularly in patients who are at risk of contracting tuberculosis.**

Tuberculosis of the conjunctiva is a rare condition. The first case was reported by Koester in 1873.[1] Eyre reviewed 206 cases which had been reported over a 30-year period from 1882 to 1912, with a further personal series of 24 cases.[2] Lundsgaard reported 48 cases in 1915 and Igeisheimer another 22 cases in 1922.[1] There have been subsequent isolated reports.[3-16]

### Case report

A 25-year-old Zulu woman was referred with a six-month history of conjunctivitis of the left eye associated with an ulcer adjacent to the left nares. She had no other complaints and had previously been well. She had been treated with chloramphenicol ointment for three weeks, with no improvement.

On examination the visual acuity in the right eye was 6/6 and in the left eye was 6/12. The right eye was normal. There was a left-sided conjunctivitis with a mucopurulent discharge, with superficial ulceration of the lower lid margin, obliteration of the punctum, and cicatricial entropion of the lid (Fig 1). The lower third of the cornea showed mild superficial stromal scarring, with a Hudson-Stahli ferritin line. The eye was otherwise normal. There was no palpable preauricular or other regional lymphadenopathy. There was a chronic superficial ulcer of the skin under the left nares (Fig 2). The nose and throat were normal. The skin lesion was thought most likely to be lupus vulgaris, and a provisional diagnosis of primary tuberculous lupus vulgaris with an associated tuberculous conjunctivitis was made.

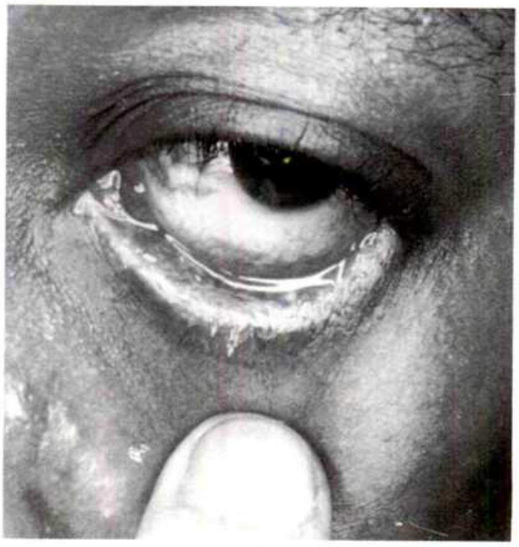

*Figure 1: Left sided chronic conjunctivitis with ulceration of the lid margin.*

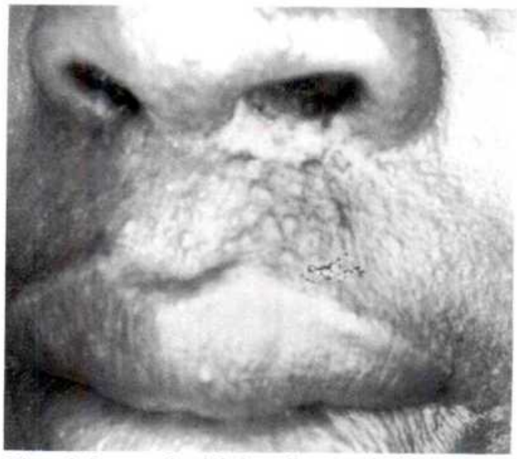

*Figure 2: Lupus vulgaris lesion adjacent to the left nares.*

The conjunctival swab yielded *Staphylococcus aureus* on culture, sensitive to chloramphenicol. No acid-fast bacilli were seen on microscopy. Treatment with chloramphenicol ointment was given for one week, with no improvement. The Mantoux test was strongly positive. The chest x ray was normal. Biopsy specimens were taken from the skin lesion and the conjunctiva. Histology of the skin lesion showed appearances consistent with lupus vulgaris, with tuberculoid granulomata being present in the papillary dermis (Figs 3A, B). Histology of the con-

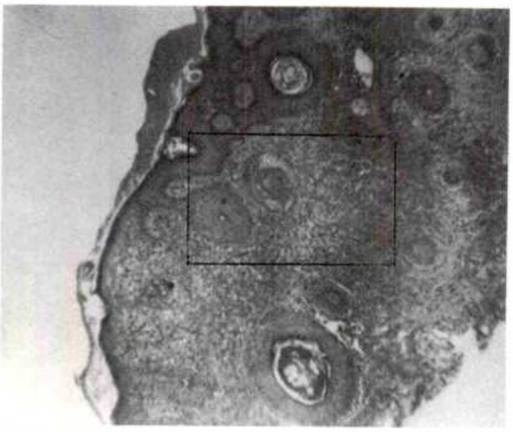

*Figure 3A: ×20.*

*Figure 3: Histology of the skin lesion, showing a tuberculoid granuloma. (H and E.)*

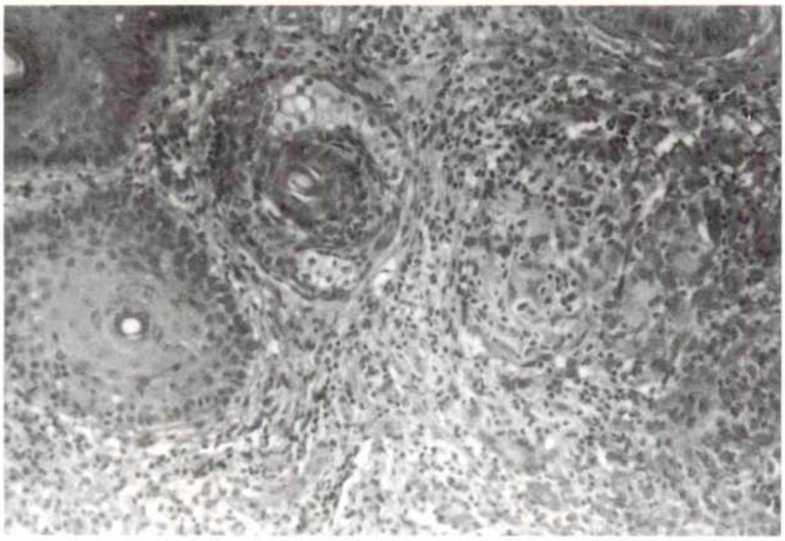

*Figure 3B: ×85.*

junctiva showed appearances consistent with tuberculous conjunctivitis, with tuberculoid granulomata being present (Figs 4A, B). No acid-fast bacilli were seen on histological examination.

The patient was treated with a standard antituberculous regimen of rifampicin 450 mg daily, isoniazid 400 mg daily, and pyrazinamide 1·5 g daily for six months. The skin lesion and conjunctivitis resolved on this treatment after one month.

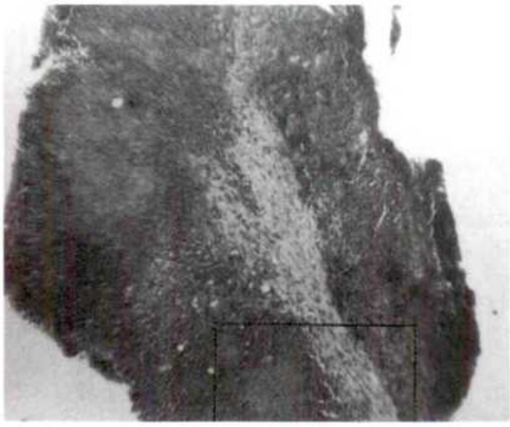

*Figure 4A: ×20.*

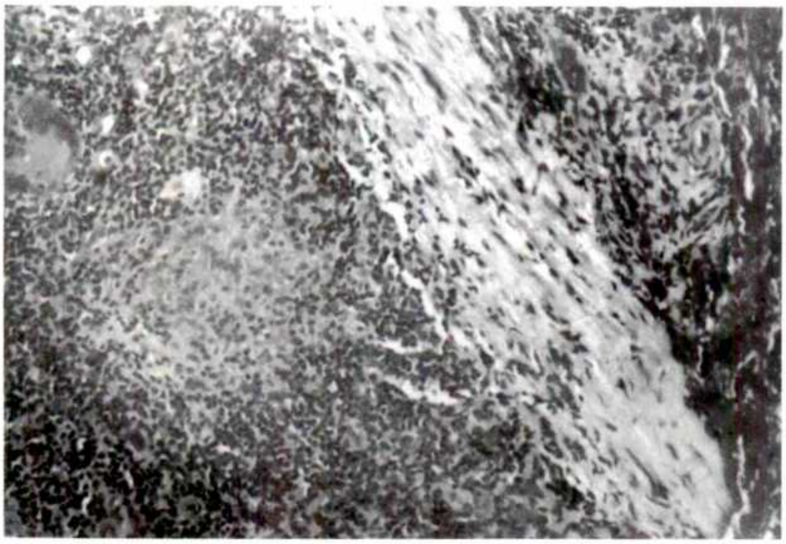

*Figure 4B: ×85.*

*Figure 4: Histology of the conjunctiva, showing multiple tuberculoid granulomata. (H and E.) 32×. Inset 100×.*

## Discussion

Primary tuberculous conjunctivitis occurs as a result of an exogenous infection. There are five clinical types – ulcerative, nodular, hypertrophic, granulomatous, and pedunculated. It may occur more commonly in young than old patients, and may be associated with regional lymphadenopathy. It runs a chronic course, and may heal with scarring or may spread to involve adjacent tissues and structures.

Secondary tuberculous conjunctivitis occurs as a result of spread of infection from a contiguous focus. There are six clinical types – ulcerative, nodular, hypertrophic, granulomatous, pedunculated, and lupoid. It may occur more commonly in adults than children and may not be associated with regional lymphadenopathy.[1]

In both instances, the diagnosis is confirmed on histological examination. Treatment is with systemic antituberculous therapy, and there is usually rapid resolution of the conjunctivitis on this therapy.

Our patient showed features of a conjunctivitis occurring in association with a neighbouring, but not contiguous, lupus vulgaris lesion. While the diagnosis of tuberculosis was suggested in our patient by the lupus vulgaris skin lesion, the clinical picture of tuberculous conjunctivitis may be sufficiently varied as to make a clinical diagnosis difficult. It is therefore necessary to consider it in any unusual chronic conjunctivitis, with or without regional lymphadenopathy, particularly in patients living in communities where the incidence of tuberculosis is still high.

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# A case of miliary tuberculosis with disseminated choroidal haemorrhages

Takashi Shiono, Shin-ichi Abe, Toshio Horiuchi

**Abstract**

**A 20-year-old Japanese man had generalised miliary tuberculosis. Although he had no ocular symptoms, choroidal miliary tuberculosis with pleomorphic findings, including disseminated choroidal haemorrhages, was noted in both fundi. The haemorrhages disappeared as the patient's condition improved on medical therapy. Disseminated choroidal haemorrhages should be looked for in patients with miliary tuberculosis.**

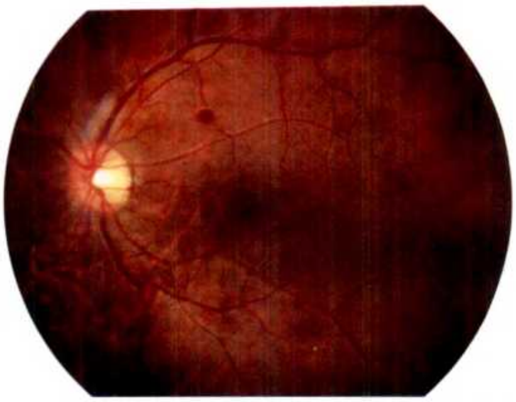

*Figure 2: Left eye: disseminated choroidal haemorrhages and one retinal haemorrhage.*

Uveal involvement has been described in primary, recurrent, and miliary forms of tuberculosis.[1-6] Although common ocular findings of the disease are uveitis and choroidal tuberculoma, these changes are often pleomorphic, and the roles of bacteriological and immunological variables are unknown.[1-6] The diagnosis of tuberculosis implies the need for appropriate systemic therapy. We treated a man with miliary tuberculosis and disseminated choroidal haemorrhages. The haemorrhages disappeared as the patient's general condition improved with chemotherapy.

## Case report

A 20-year-old Japanese man was admitted to the hospital on 28 April 1986 with a two-month history of cough, fever, and chills. He had been diagnosed as having nephrotic syndrome in October 1985 and had been taking a steroid since then.

A chest *x* ray film taken on admission to hospital revealed pleuritis. Echography of the abdomen showed hepatosplenomegaly. A computed tomographic scan of the brain disclosed multiple disseminated dense lesions. Cultures of the sputum and pleural effusion were positive for *Mycobacterium tuberculosis*. The diagnosis of generalised miliary tuberculosis was made. The following laboratory findings were noted: white blood cell count (WBC), $4{\cdot}4\times10^9$/l; red blood cell count (RBC), $4{\cdot}1\times10^{12}$/l; haemoglobin (Hb), 10·5 g/dl; haematocrit, 32·3%; platelet count, $411\times10^9$/l; bleeding time, 5 min 30 s; coagulation time, 8 min.

The patient was treated with isoniazid (750 mg/day), rifampicin (450 mg/day), and ethanbutol (750 mg/day). Three months later he was referred to our clinic for ocular side effects of ethanbutol; his condition had improved with the treatment and he had no ocular symptoms.

Ocular examination on 28 July 1986 showed a best corrected visual acuity of 20/20. The intraocular pressure was 18 mmHg in both eyes. He had normal ocular movements and normal pupillary reactions. No abnormal findings were noted in the anterior segment, lens, or vitreous of either eye. Ophthalmoscopic examination of the right eye showed a small white lesion inferotemporal to the macula (Fig 1). In the left eye multiple disseminated dark-red haemorrhages with blurred margins were noted in the posterior pole (Fig 2). The retinal vessels coursed over the haemorrhages. These findings suggested that the haemorrhages were in the choroid. In addition

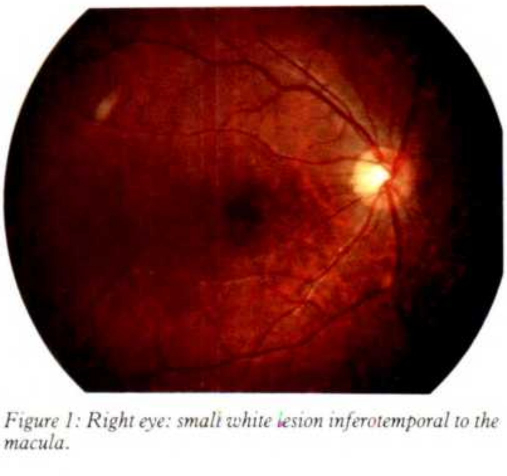

*Figure 1: Right eye: small white lesion inferotemporal to the macula.*

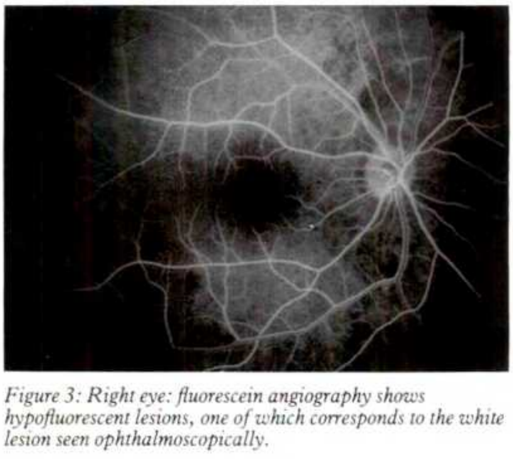

*Figure 3: Right eye: fluorescein angiography shows hypofluorescent lesions, one of which corresponds to the white lesion seen ophthalmoscopically.*

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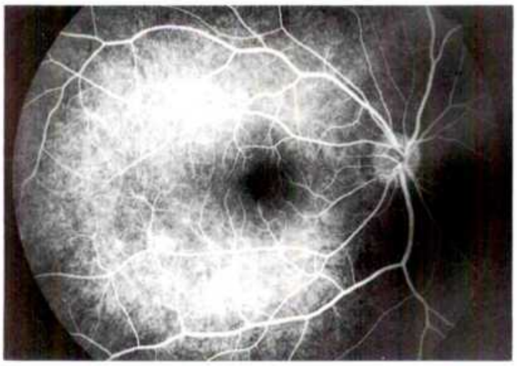

*Figure 4: Right eye: the lesions hyperfluoresce in the late phase.*

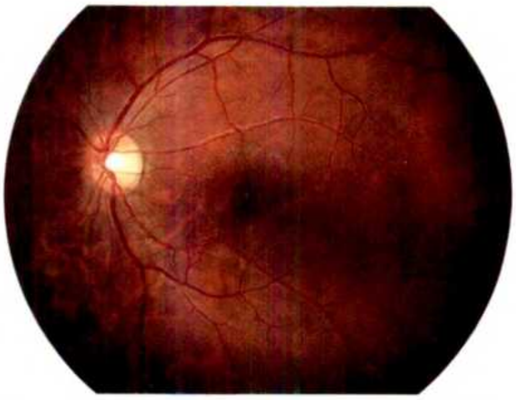

*Figure 6: Left eye: after four months the haemorrhages have disappeared.*

one retinal haemorrage was noted in the upper region of the macula. Fluorescein angiography of the right eye revealed focal areas of hypofluorescence in the early phase, one of which corresponded to the white lesion seen ophthalmoscopically inferotemporal to the macula (Fig 3). Later the lesions hyperfluoresced (Fig 4). In the left eye there were disseminated hypofluorescent lesions corresponding to the haemorrhages and focal areas of hyperfluorescence (Fig 5) that enlarged with time. A haemogram at that time showed the following values: WBC, $7{\cdot}5\times10^9$/l; RBC, $3{\cdot}9\times10^{12}$/l; Hb, 10·2 g/dl; haematocrit, 31·0%; and platelet count $359\times10^9$/l. In one month the patient's general condition improved and the haemorrhages in the left eye began to disappear. Four months later no haemorrhages were seen ophthalmoscopically (Fig 6). However, fluorescein angiography revealed areas of hyperfluorescence with sharper margins than before (Fig 7). No ophthalmoscopic changes in the right fundus were observed during that time.

## Discussion

Acute miliary tuberculosis results from bacteraemia in a person whose resistance is low, such as our patient who was taking a steroid. The ophthalmoscopic form of tuberculosis usually consists of nodules or tubercles that are greyish or white, have indistinct borders, and vary in size from one-sixth to two-thirds of a papillary diameter.[1-3 5 7 8] Angiographically the lesions are hypofluorescent initially, then show a hyperfluorescence that increases in size.[2 5 7 8] With time the lesions resolve, leaving a scar with or without pigmentation. The scars also are hyperfluorescent and have sharp margins. The lesions observed in our patient's right eye corresponded to tubercles. The hyperfluorescent lesions seen in the left eye also seemed to correspond to small tubercles.

To our knowledge no reports have appeared on disseminated choroidal haemorrhages in miliary tuberculosis. Our patient had been on a regimen of isoniazid (750 mg), rifampicin (450 mg), and ethanbutol (750 mg) daily. The therapy controlled the systemic miliary tuberculosis. There have been reports[9 10] of retinal haemorrhages with use of ethanbutol, but the choroidal and retinal haemorrhages in our patient resolved as his systemic condition improved with therapy, which included ethanbutol. The results of laboratory data were within normal ranges. These haemorrhages thus appeared to be caused by miliary tuberculosis and were not a side effect of ethambutol therapy.

There has been a report[2] of generalised miliary tuberculosis with retinal haemorrhages. We believe that miliary tuberculosis should be suspected in patients with disseminated choroidal haemorrhages, particularly in association with fever of unknown aetiology.

We thank Professor M Tamai from the Department of Ophthalmology, Tohoku University, for his helpful discussion and Ms M Gere for her review of this manuscript.

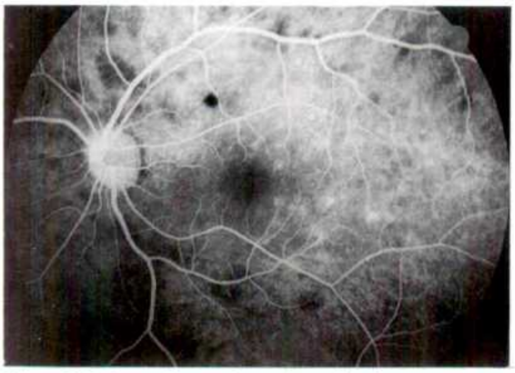

*Figure 5: Left eye: fluorescein angiography shows hyperfluorescence that corresponds to the choroidal and retinal haemorrhages. Hyperfluorescent lesions also are seen temporal to the macula.*

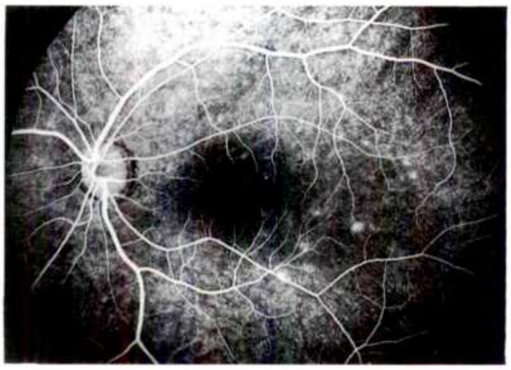

*Figure 7: Left eye: fluorescein angiography discloses small hyperfluorescent lesions with sharp margins.*

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# LETTERS TO THE EDITOR

## Corneal amyloidosis

SIR,—In their recent interesting paper Watts and Frank[1] reported a case of secondary localised amyloid of the cornea, due to chronic irritation from a scarred lid. Referring to Yanoff and Fine,[2] they stated that primary localised amyloidosis is found in the form of small red nodules in the conjunctiva and lids and as lattice corneal dystrophy.

It is worth pointing out that primary localised corneal amyloid deposits can also occur in polymorphic amyloid degeneration,[3] gelatinous drop-like dystrophy,[4] and primary familial amyloidosis of the cornea[5] (though this condition is probably an occidental description of gelatinous drop-like dystrophy, first described in the Japanese literature).

In this department a 61-year-old man recently underwent penetrating keratoplasty in the left eye for corneal scarring and central thinning which progressively occurred over the previous 13 years. Over this time his visual acuity in the affected eye diminished from $^{6}/_{18}$ to $^{1}/_{60}$. This was presumed to be due to long-standing and recently quiescent herpes simplex keratitis. His visual acuity and cornea of the right eye are normal, he has no family history of eye disease, and he has no evidence of systemic disorder. Histological examination showed a dense central subepithelial deposition of amyloid, which stained positively with Congo red and gave an apple green birefringence with polarised light. The pattern of distribution was reported as being morphologically similar to gelatinous drop-like dystrophy, though such a diagnosis is unlikely because this autosomal recessive condition is bilateral, the initial changes tend to occur in the first decade of life, and early on in the disease changes similar to band keratopathy occur.[6] Whether this is a case of secondary localised corneal amyloid secondary to long-standing herpes simplex or primary localised corneal disease of unknown aetiology remains to be elucidated, though it has suggested that such changes can be age related.[7]

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1 Watts J, Frank H. Corneal amyloidosis. *Br J Ophthalmol* 1989; 73: 674–6.
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SIR,—Thank you for pointing out that there are other reports of primary localised corneal amyloid deposits, which have been reported in the literature, mostly several years ago, and about which we were aware. The case that we reported was particularly interesting, as we were not aware that there had been any previous reports of corneal amyloidosis developing secondary to a lid defect. My comment on the case that Mr John Bell reports is that, as this describes the development of amyloid in one eye, it is unlikely that this represents a primary amyloid degeneration. In all the reports quoted by Mr Bell four cases of primary amyloidosis affected both corneas, as would be expected in any dystrophic condition.

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# BOOK REVIEWS

**Movements of the Eyes.** 2nd Edn. By R H S Carpenter. Pp 593. £59.50. Pion: London, 1988.

The second edition of this textbook, the first edition of which was produced in 1977, is divided into three sections. The first section is on the function of eye movements and covers in a clear and easy-to-understand fashion, the purpose of eye movements and the characteristics of vestibular, optokinetic, pursuit, and saccadic movements. In addition there are useful sections on vergence and on miniature movements.

Section 2 is on structure of the ocular motor apparatus and includes sections on the statics and dynamics of the eye, on the extraocular muscles and their innervation, and on the central pathways controlling ocular movement.

Section 3 is on the system as a whole and concerns proprioception and its role in the control of eye movements, the role of vision in modification and control of eye movements, adjustments to the ocular motor system, and then a synthesis of all the understanding currently available as to how the eye movement control system actually works in a biophysical fashion.

This is an excellent book. It is notably clear in its explanations and is quite comprehensible to the non-specialist, who will find much in it to appreciate and understand. The diagrams are clear and the book is well written in an informal and engaging style. The tendency is to approach structure from the point of view of comparative anatomy rather than from the point of view of neurological lesions, which is perhaps more the way in which ophthalmologists have tended to be taught this information in the past.

There are several useful appendices. There is one up-to-date and very helpful section on the methods of measurement of eye movements. There is also what appears to be an excellent introduction to systems analysis, which seems clear and well written and has the minimum of mathematics, but I am sorry to say that it was somewhat wasted on this reviewer. Finally there is a simple glossary and index of terminology. The bibliography runs to 94 pages of references and the index is very good.

This may not be a book for the individual ophthalmologist, but I cannot imagine any ophthalmological or indeed physiological library which could manage without it, for it deals with an ever expanding field of medical and basic science research.

J P LEE

**Wenner-Gren International Symposium Series.** Vol 49. **Strabismus and Amblyopia.** Eds Gunnar Lennerstrand, Gunter K von Noorden, Emilio C Campos. Pp 438. £50. Macmillan: Basingstoke, Hants. 1988.

This book contains the proceedings of an international symposium held in Stockholm in June 1987 to which an international group of experts, both basic scientists and clinicians, were invited. The editors refer in the introduction to the workshop character of the meeting, and the very full discussion is printed alongside the papers.

The book is divided into three sections. The first is on ocular motor control and strabismus, and among the topics considered are the aetiology of infantile esotropia, developmental abnormalities in strabismus and amblyopia, vergence mechanisms, and extraocular muscle abnormalities in strabismus. The second section is entitled 'Normal and abnormal visual development' and is chiefly concerned with aspects of amblyopia and its pathophysiology. The third section is entitled 'Psychophysics related to strabismus and amblyopia'. Among other things this contains interesting material on proprioception, both from an experimental and clinical point of view. There are also parts within this section on stereopsis and clinical aspects of amblyopia and the book ends with a review by Julesz on stereopsis.

The symposium provides up-to-date clinical and basic science of interest to the specialist in the field, but not to the generalist. Basic science and clinical workers have a long way to go in this field before each understands what the other is saying, and this matter is alluded to wittily in the introduction by Professor Tengroth. His point is that we still do not have a synthesis, but we have made considerable strides since the last of these symposia was held in 1974, and I would be inclined to agree with him.

J P LEE

---

## Correction

In the recent paper by Williams and Mieler (*Br J Ophthalmol* 1989; **73**: 985–90), Figures 3A and 3C were unfortunately transposed, and Figure 3C (which should have been 3A) was printed upside down.

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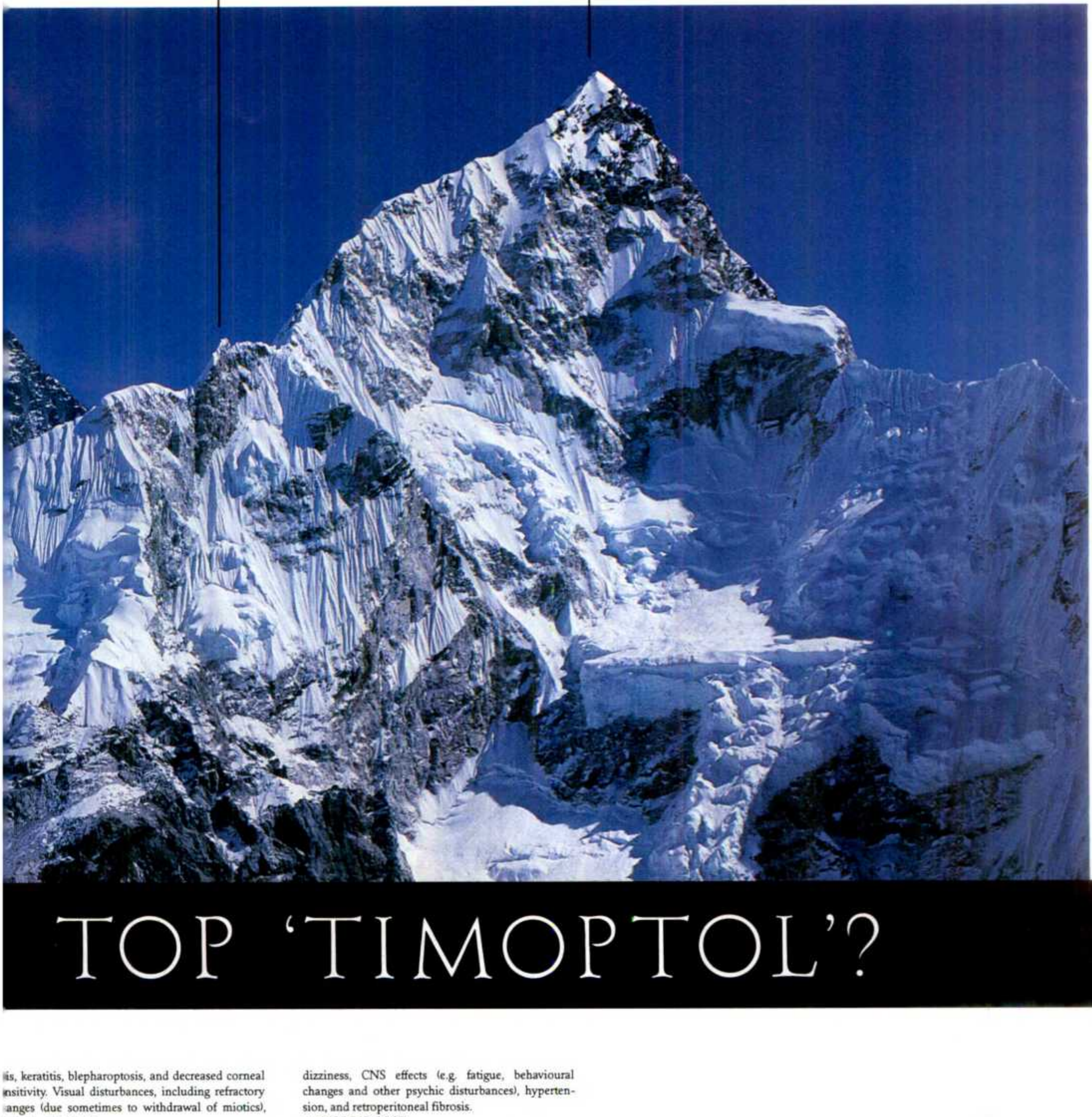

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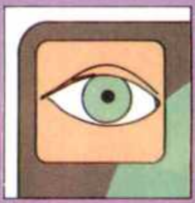

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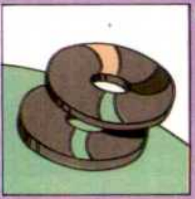

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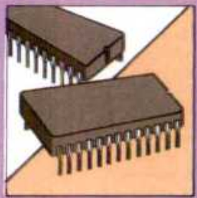

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*British Journal of Ophthalmology*, 1990, 74, 321–322

BRITISH JOURNAL OF OPHTHALMOLOGY

## *Editorial*

# Lyme disease

Lyme disease takes its name from a town in New England where an outbreak of chronic arthritis in children was studied and reported in 1977. Epidemiology suggested a tick borne infection, and in 1982 the causative organism, a previously unrecognised spirochaete, was found and named *Borrelia burgdorferi*. Since then the disease has become more widely recognised as a result of clinical awareness, better diagnostic tests, and an increase in deer stocking.[1] It is now the commonest tick borne infection in the USA, with over 6000 reported cases in 1987. The tick is widely distributed, and variants of the disease have been described in Europe since early this century. A rise in cases is now being reported in Britain for similar reasons as in the USA.[2]

*Borrelia burgdorferi* is transmitted by ixodes ticks. The tick's life cycle is not fully documented, but in New England it depends on the white footed mouse for its larval and nymphal stages and the white tailed deer as the preferred adult host, though West Coast ticks are apparently happy to substitute lizards for mice. The spirochaete lives in the gut of the tick and is injected into the unfortunate host through its saliva. Ixodes ticks are widely distributed throughout America, Europe, and Asia, and the spirochaete can be found in mosquitoes and deer flies as well, though the importance of these to human disease is unknown.

Lyme disease is a multisystem disease with major cutaneous, neurological, cardiac, and rheumatological manifestations. For a complete and authoritative review of the disease and all its ramifications readers should consult the review by Steere,[1] who described the original cases in 1977. The disease has similarities to syphilis, with stages of localised infection, dissemination, and late persistent infection. Ocular involvement is uncommon and occurs mainly in the second stage. Following inoculation of the spirochaete by a tick bite patients develop a characteristic skin lesion, erythema migrans (stage I), usually centred on the tick bite, and they may develop fever, lymphadenopathy, and constitutional symptoms. Conjunctivitis has been reported in 11% of patients. Dissemination (stage II) is by blood or lymphatic spread. Secondary annular skin lesions appear, and the patient may be quite ill with fever, malaise, and fleeting musculoskeletal pains. After several weeks or months 15–20% of patients in the USA have developed neurological symptoms, of which chronic lymphocytic meningitis, cranial polyneuropathy, or radiculitis are the commonest; 4–8% develop cardiac symptoms, with arrhythmias or myopericarditis. After six months about 60% of patients develop arthritis of major joints (stage III), particularly the knees. Apart from chronic arthritis a progressive encephalomyelitis and a skin disorder known as acrodermatitis chronica atrophicans can occur at this time. Congenital infection has been reported, usually with a fatal outcome for the fetus.

Ocular involvement can be seen as conjunctivitis in stage I but occurs more commonly in stage II; a keratitis may be seen in stage III. Ocular involvement appears to be relatively infrequent. The commonest findings are a uveitis or endophthalmitis, oculomotor palsy, or papilloedema from meningeal involvement.

Most descriptions of ocular disease concern sporadic case reports, but Kinward *et al* have recently reported a series of six cases with ocular involvement.[3] The patients' ages ranged from 11 to 71 years; five of the six had visited endemic areas for Lyme disease but only two had a positive history of a tick bite. Five of the six patients had a bilateral vitritis, with similarities in one to pars planitis; the other patient had a fourth nerve palsy. Three of the six patients had a facial nerve palsy, the commonest cranial neuropathy found with Lyme disease. The most important lesson from these cases is that recognition of Lyme disease led to appropriate antibiotic treatment and a good visual outcome. Other ocular manifestations are ischaemic optic neuropathy, optic neuritis, and optic disc swelling with or without raised intracranial pressure, as well as oculomotor palsies. These are reviewed in the discussion of a patient with unilateral endophthalmitis from Lyme disease in this issue of the *BJO*.

The various manifestations appear to be related to direct infection with the spirochaete, which can be recovered histologically or cultured with varying degrees of success from involved organs. Most cases are, however, diagnosed serologically using an ELISA test. This becomes positive for IgM during the first few weeks of infection, during this time false negative results can occur. An IgG response occurs later. Seronegative cases can occur; in these cases the diagnosis was made by finding a specific T cell blastogenic response,[4] and it has recently been shown that in these cases the antigen is sequestered in immune complexes.[5]

In Britain Lyme disease usually occurs in people from a rural or agricultural background. In a study of serological titres in 101 patients from Dumfries chosen because of potential exposure 12 were found to give positive results from serological tests; all were farmers, six exclusively working with dairy cattle, the others working with cattle and sheep. No patient had typical features of Lyme disease, but 11 of the 12 had symptoms such as arthritis, which might have been relevant.[6] No ocular Lyme disease has yet been reported in

Britain, though the gardener of a London ophthalmologist has apparently suffered cardiac manifestations.

*Borrelia burgdorferi* is sensitive to tetracyclines and erythromycin. These appear to be the best antibiotics for the treatment of the systemic infection, as the spirochaete is apparently less sensitive than *Treponema pallidum* to penicillin, but the best treatment for intraocular disease is not yet known. The Bascom Palmer patients with early disease did well with doxycycline, and good results in the others were obtained with intravenous ceftriaxone. The disease may relapse after treatment, and in this series all three patients who did relapse had had prior treatment with oral steroids. The role of steroids in systemic infection is controversial, in one series predisposing patients to antibiotic failure.[7] Systemic steroids are therefore probably at present best avoided in the management of patients with intraocular Lyme disease.

D J SPALTON

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# *Editorial*

## Neovascularisation again

Since the original suggestion by Michaelson in 1948 that there is probably a substance in retina which can stimulate new vessel formation[1] and the publications from Ashton's laboratory explaining the preretinal neovascularisation in retinopathy of prematurity (ROP)[2] and the more remote neovascularisation of the iris in central retinal vein occlusion (CRVO)[3] in terms of retinal hypoxia, many experiments have been carried out in attempts to elucidate the mechanisms involved. The probability that the hypoxia theory is correct was much increased by the classical work of Laatikainen and Kohner,[4] who showed that neovascularisation occurred in CRVO only when retinal capillary closure could be identified by fluorescein angiography. Meanwhile the search for a substance to incriminate had already begun. Numerous clinical studies were carried out over the years, not to mention the rise of retinal ablation as a means of treatment for diabetic retinopathy[5] and neovascular glaucoma.[6]

One of the earliest substances to come under suspicion was lactic acid.[7] Intravitreal injections of lactic acid were given repeatedly to young kittens, of which 50% developed intravitreal vasoproliferation. Later attempts to confirm this by demonstrating excess lactic acid in the vitreous of kittens and rats whose retinas had been rendered ischaemic were unsuccessful,[8] and lactic acid seems to have been dropped. In 1978 Patz and coworkers[9] made the interesting observation that tumour cells introduced into rabbit vitreous produced neovascularisation only when in contact with vascularised retina and suggested that there may normally be an antineovascularising substance present in rabbit vitreous. It is worth mentioning that as well as studies on the subject of preretinal intravitreal and even iris new vessels interest was also being taken in subretinal neovascularisation, since this is just as important a field as the others and probably concerned with similar pathological processes. Miller and colleagues,[10] for example, thought that the retinal pigment epithelium might play a part in inhibiting new formed subretinal vessels, but, although there does not seem to be a convincing theory as to the causation of subretinal neovascularisation, nevertheless the possibility that the pigment epithelium has some sort of active role has continued to arouse interest.

There was something of a setback in 1977 when Kissun and Garner[11] were unable to prove that extracts of ischaemic kitten retina would induce excess neovascularisation in experimental corneal tunnels, but in 1980 Federman and coworkers[12] succeeded in inducing corneal vascularisation by retinal implants, and in 1982 Kissun and colleagues[13] found similar results in chorioallantoic membrane test beds using extracts of healthy adult cat retina. They proposed a low molecular weight angiogenic factor, which seems to be similar or possibly the same as the endothelial cell stimulating angiogenic factor (ESAF) which was originally described in tumour angiogenesis. They pointed out that, whereas clinically neovascularisation seems to occur only in response to retinal ischaemia, the angiogenic factor appears to be present in healthy retina. This puzzle can be explained by postulating that there is also an antivascularising substance present which is normally in equilibrium with ESAF. Neovascularisation in disease or regression of neovascularisation as a result of therapy may therefore be expressions of alterations in this balance rather than the production or reduction of a single substance. In 1986 Taylor and coworkers carried the story further when they demonstrated significant levels of an ESAF-like substance in the retinas of oxygen deprived kittens[14] and in 1988 increased levels in the vitreous humour.[15]

Parallel with these studies have been tissue culture experiments where the properties of retinal extracts can be studied in the laboratory in rather a precise and elegant manner. Wong and colleagues[16] have shown that tissue-culture media conditioned by extracts of retinal pigment epithelial cells stimulate the proliferation of retinal capillary endothelial cells as well as pericytes. However, in a paper in the *BJO* this month Singh and colleagues show that exactly the opposite effects are seen in tissue culture when the system is conditioned by vitreous from eyes which had been subjected to extensive retinal destruction by laser. This appears to be further evidence for the retina's balancing act between neovascularisation and vascular stability, and the authors proffer it as a possible explanation for the beneficial antineovascularising effect of retinal ablation.

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British Journal of Ophthalmology, 1990, 74, 324

## *Editorial*

# Not enough cataract surgeons

Just over a year ago an editorial entitled 'Blindness in two worlds' was published in the *BJO*,[1] and we make no apology for returning to this important subject again, this time in response to articles on blindness and eye disease in Kenya and India. The previous editorial dealt with the contrast between the results of a survey of blindness and low vision in The Gambia[2] and two surveys of blindness in the United Kingdom – in Bristol and in Leicester.[3 4] As would be expected, there were considerable differences, the burden of blindness being heavier in the African study and the causes being differently distributed, so that, for example, cataract and corneal disease accounted for the majority of African blindness whereas in the UK macular disease was the chief aetiological factor.

So what is new about the present studies? Sad to say the answer is not very much.

The Kenyan study method, described as random cluster sampling, was similar to that used in The Gambia, though the total number of people examined was greater, at 13 803 compared with 8174 in The Gambia. Fairly substantial differences in prevalence for the principal causes of blindness show up in the figures. For example, cataract accounts for 36% of all blindness in Kenya compared with 55% in The Gambia, and corneal scarring, with or without trachoma, for about 15% compared with 37%. In contrast to The Gambia, where retinal disease made hardly any impact on the figures, Kenya has approximately as many blind from retinal disease as corneal, rather a surprising finding. Both studies report substantial visual impairment due to refractive error, a good proportion of which is probably uncorrected aphakia.

In spite of these differences, which are probably due to a variety of circumstances, the total of blindness comes out at exactly the same figure for each country as a whole, 0·7% of the population. One is getting used to this figure for blindness in Third World countries, but it is terrifyingly high if compared with the 'developed' world at around 0·2%.

The introductory paragraph to the current Kenya paper sets out the problems very well, though one is surprised to read the claim that blindness rates in poor countries are often '10 to 20 times those in industrialised nations'. Even if we reduce this somewhat to an average difference of, say, three to four times the rate, there is clearly a huge task ahead if the difference is to be reduced.

As is confirmed in the Indian study cataract is the main problem. Although there is a possibility that the burden of cataract may be reduced in future as aetiological factors become gradually better understood, such hopes certainly do not apply to the immediate future and cannot apply to those already suffering from cataract. As noble initiatives to enable the underprivileged and the undernourished to survive in spite of war, drought, and famine are introduced by the numerous relief agencies and energetic individuals devoted to this cause, so does the number of cataracts, present and future, increase as the populations increase. And in spite of the ever swelling chorus of (mostly ill informed) criticism of orthodox medicine there is little dissent from the present view that the only way cataract can be effectively treated in 1990, and probably for at least the rest of the decade, is by surgery. Virtually anyone concerned with world blindness agrees with this opinion; the difficulty is to organise matters so that the surgery can be made available for the huge number of people who need it. The International Eye Foundation and the Royal Commonwealth Society for the Blind are examples of two organisations devoting time and resources to the problem, but there are many others too numerous to name which are also trying in various ways to improve the situation.

When we were young the cataract problem was mostly a matter of 'how to do it' to get the best and most reliable result. The means to these ends consisted of learning the appropriate techniques and acquiring by practice the requisite manual dexterity. We were also, it has to be admitted, usually worried to a greater or less extent whether we would ever arrive at the position of consultant in the UK (or its equivalent rank in other countries), so that there would be an opportunity to perform cataract extractions on our own patients. The thought that there were millions of patients scattered about all over the world worrying about whether there would ever be an ophthalmologist available to remove their cataracts never entered our heads. We may have to rethink our attitude now. As a start it could well be useful, and I am sure this or something like it has been suggested and even practised many times before, for training authorities to consider an overseas elective as, if not compulsory, at least highly desirable.

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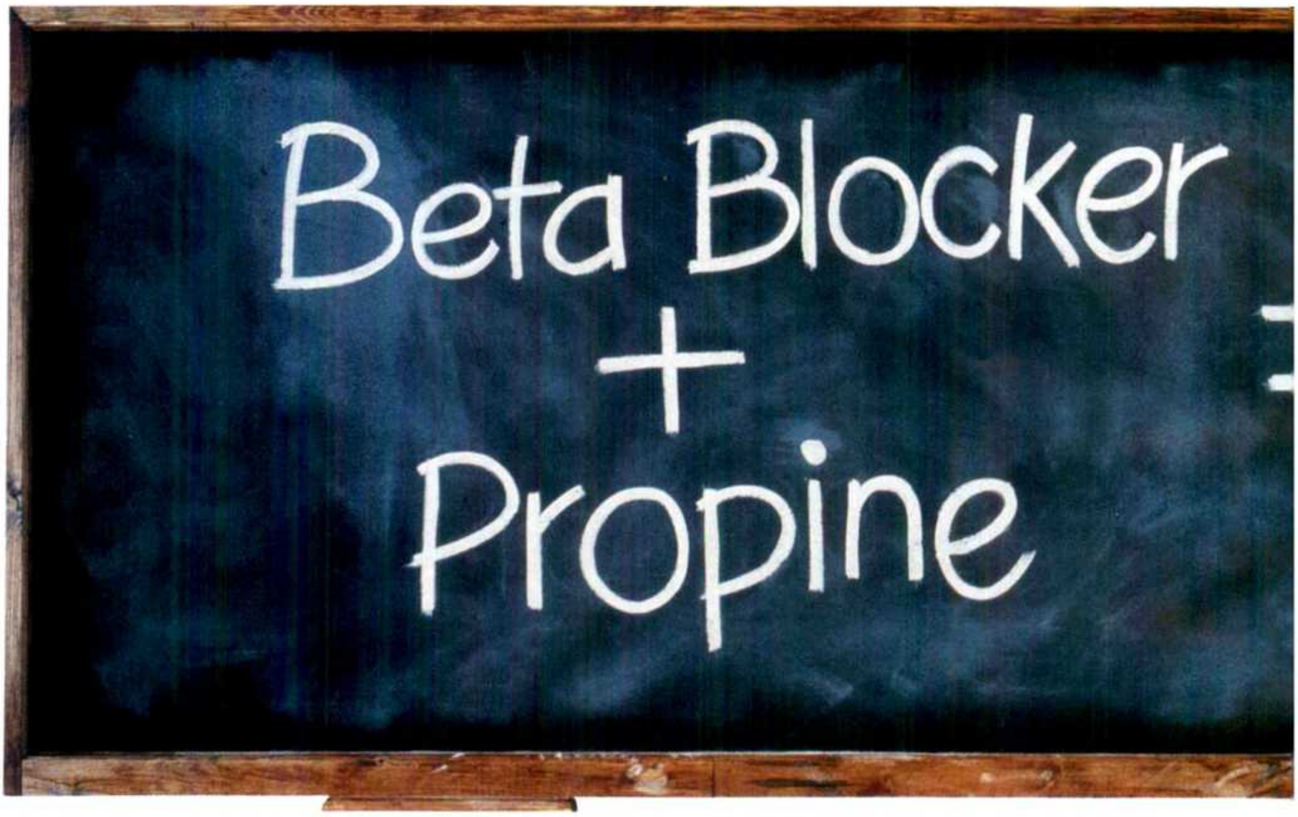

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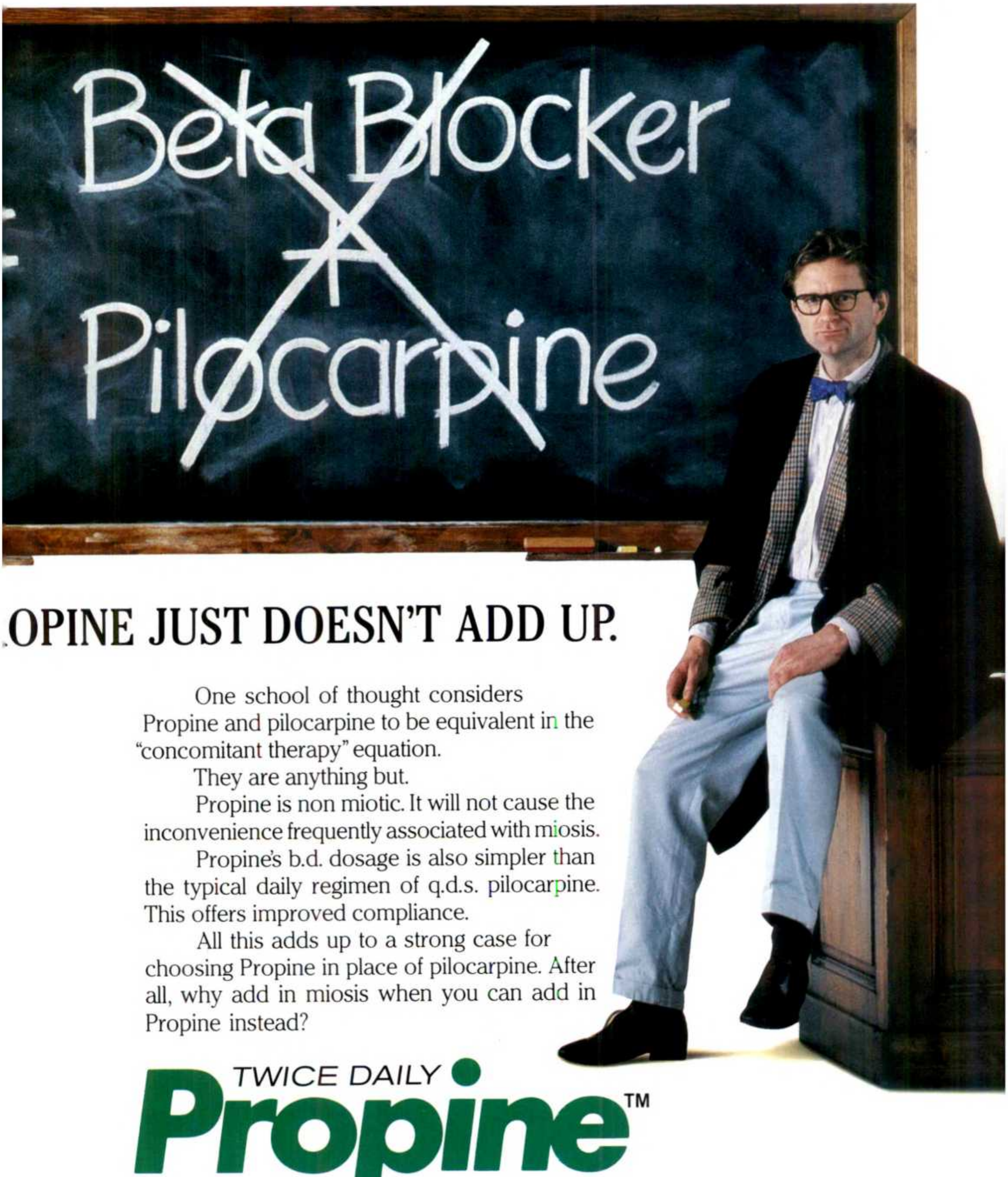

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ORIGINAL ARTICLES

# Ocular Lyme disease: case report and review of the literature

Danny J H Kauffmann, Gary P Wormser

**Abstract**
**Lyme disease is an emerging new spirochaetal disease in which ocular complications may arise. We have seen a 45-year-old woman who developed unilateral endophthalmitis leading to blindness during the course of this disease. Ocular tissue showed the characteristic spirochete. A literature review shows that the commonest ocular manifestation of Lyme disease is a mild conjunctivitis, but other symptoms may include periorbital oedema, oculomotor palsies, uveitis, papilloedema, papillitis, interstitial keratitis, and others. Ophthalmologists treating patients from Lyme disease endemic areas need to be aware of the protean clinical manifestation of this disease.**

Lyme disease, a tick-borne spirochaetal infection,[1] often begins with a characteristic rash, erythema chronicum migrans.[2 3] Ocular manifestations have been infrequently reported, but, as the disease is increasing in frequency and occurring in new geographical areas,[4] more cases with ocular involvement can be expected. We report in detail the eye findings in a patient previously reported on who developed severe, unilateral endophthalmitis five weeks after erythema chronicum migrans.[5] Spirochaetes were found in the vitreous in specimens obtained at surgery. In addition we review the literature of the ocular and neuro-ophthalmic manifestations of Lyme disease.

## Case report

On 15 July 1982 a 45-year-old woman from Westchester County, New York, developed severe headache, light headedness, chills, and fever. Three days later she also had nausea and vomiting. On 21 July she noted red lesions on her right foot and upper arms that looked like insect bites. In addition a large annular erythema with an indurated centre was noted on the right thigh. This lesion expanded and developed a bright red outer border with central clearing. She remembered having been bitten by many flying insects during the 4 July weekend but recalled no tick bites. She was treated with diphenhydramine hydrochloride 50 mg four times a day and a cortisone skin ointment for what was thought to be a local skin allergy to insect bites. On 30 July, because of daily fevers, malaise, and skin lesions, she was admitted to a community hospital.

A physician removed fragments of a presumed insect stringer from her right foot accompanied by a white mucoid discharge. Her white blood cell count was $22\times10^9/l$ with 73% polymorphonuclear leucocytes and 18% band forms, and the erythrocyte sedimentation rate was 48 mm/h. She was treated empirically with intravenous cefazolin, 6 g a day for seven days, but continued to have daily fevers up to 40·1°C (104·2°F). She was then changed to oral tetracycline, 500 mg four times a day for seven more days. She responded well to this regimen.

Two weeks later, on 25 August 1982, a sting on the left thigh by a bee caused local erythema. Two days afterwards she awoke with a painful red left eye. She had no eye complaints previously. The patient treated herself with sulphafurazole (sulfisoxazone) drops, but sought an ophthalmologist when the vision decreased in the left eye and periorbital oedema developed. She was noted to have iritis and posterior synechiae and was treated with topical atropine 1% and Predforte 1% (dexamethasone) drops, with resultant breaking of the synechiae. However, the iritis persisted, and despite subconjunctival injection of triamcinolone 40 mg hypopyon developed along with vitritis. Oral prednisone 60 mg per day was begun. The visual acuity nevertheless worsened, and the prednisone dose was increased to 100 mg daily. She was then transferred to Westchester County Medical Center.

Her visual acuity was 20/20 right eye and hand motions left eye. The results of ocular examination including tension were normal in the right eye. The left eye showed mild conjunctival ecchymosis and ciliary vessel injection. There was mild periorbital oedema. The ocular rotations were full, though splinting of the left eye was noted in extreme fields of gaze. There was no measurable proptosis. The cornea showed microscopic epithelial oedema with stippled fluorescein staining. There was a severe inflammatory reaction in the anterior chamber, with 3+ flare and cells, and a 20% hypopyon was present. After dilatation of the pupil pigment residua were noted on the anterior lens surface from the previously treated posterior synechiae. The lens was otherwise clear. The ocular tension was 18 mmHg. The left fundus could not be seen, and no red reflex was obtained through the cellular debris in the media. Ophthalmic A and B scan ultrasound revealed diffuse debris in the vitreous cavity, with marked thickening of the choroid consistent with a

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TABLE I *Ophthalmic and neuro-ophthalmic manifestations of Lyme disease*

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| Optic neuritis |
| Optic perineuritis |
| Ischaemic optic neuropathy |
| Optic atrophy |
| Cranial nerve palsies |
| Argyll-Robertson pupil |
| Pupillary areflexia |
| Horner's syndrome |
| Cortical blindness |
| Papilloedema |
| Conjunctivitis |
| Keratitis |
| Iritis |
| Iridocyclitis |
| Panuveitis |
| Vitritis |
| Choroiditis |
| Exudative retinal detachments |
| Retinal vasculitis |
| Retinal haemorrhages |
| Periorbital oedema |

severe panophthalmitis. The retina was attached.

The initial impression was severe uveitis of unknown aetiology. Prednisone was continued at 100 mg daily and tapered to 60 mg over the next seven days. Roentgenograms of the chest, skull, sinuses, orbits, and sacroiliac joints were normal. Serological tests for syphilis (FTA-abs, VDRL), antinuclear antibodies, angiotensin converting enzyme, cryoglobulins, rheumatoid factor, toxocara, toxoplasmosis, histoplasmosis, and cytomegalovirus were negative. A 5 TU tuberculin skin test was negative. Serum creatinine and liver enzymes were normal. Serum obtained on 17 September 1982 showed an IgM antibody titre to the Lyme spirochaete of 1:64 and an IgG titre of 1:512 (normal for both <1:64) determined by indirect immunofluorescence.

Eight days after admission to hospital and while on prednisone 60 mg daily the patient developed a rapid rise in intraocular pressure in the left eye to 40 mmHg along with 5 mm proptosis, a conjunctival purulent discharge, and the rapid onset of a dense cataract. Computerised tomography showed no evidence of a lesion to explain the proptosis. Orbital cellulitis was suspected, and nafcillin 12 g/day plus gentamicin 80 mg every eight hours was given intravenously along with topical neomycin-polymixin B (Neosporin) and dexamethasone. The ocular tension was controlled with acetazolamide 1 g orally daily and timolol 0·5% topically. Conjunctival cultures were negative for bacteria, fungi, and mycobacteria.

One week later, 19 days after admission, a lensectomy and vitrectomy were performed and purulent vitreous material was removed. Intravitreal gentamicin 0·2 mg in 0·1 ml and chloramphenicol 0·2 μg in 0·1 ml were injected and systemic antibiotics were maintained, while systemic steroids were tapered. Cultures and smears for bacteria, fungi, and acid fast organisms were negative, and cytological examination of a fresh vitreous specimen revealed only white cells. One week later a second vitrectomy to remove increasing amounts of vitreous debris was performed. Examination of the material by dark field microscopy was negative for spirochaetes.

Pathological examination of the lens and vitreous contents showed lens fragments and necrotic cells with a heavy infiltration of mononuclear cells. Later the eye tissue was stained by the Dieterle method.[6] Despite the advanced cell necrosis, occasional intact spirochaetes, morphologically compatible with the Lyme spirochaete, were demonstrated in vitreous material.

After surgery the patient continued to have mucous secretions from the eye and experienced occasional myalgias and arthralgias. A good red reflex was obtained, vision returned to hand motions, and on 13 October she was discharged from hospital. However, over the ensuing three months she developed a dense cyclitic membrane in her eye and lost all functional visual activity, with the eye becoming phthisical. On 28 October IgM antibody to the spirochaete was no longer detectable, and the titre of specific IgG had decreased to 1:64. By May 1983 neither specific IgM not IgG antibody was found. After one year the patient was given a cosmetic contact lens shell covering the phthisical left eye. She developed no manifestation of Lyme disease in her right eye, which continuously maintained 20/20 vision throughout the course of her disease.

## Discussion

Our patient presented with a uniocular uveitis due to Lyme disease which progressed to a panendophthalmitis and ultimate destruction of useful uniocular vision.[5] Other examples of Lyme related uveal tract involvement include case reports of patients with iritis,[7] uveitis,[8 9] and choroiditis with exudative retinal detachment.[10] The visual outcome of the other reported cases was much better. A patient with iritis had spontaneous resolution, and visual acuity in the others improved after the use of specific systemic antibiotics with[8] or without[9 10] concomitant ocular steroids.

Additional ocular manifestations of Lyme disease include conjunctivitis, photophobia, periorbital oedema, cranial nerve palsies, keratitis, pupillary abnormalities, papilloedema, optic neuritis, and optic atrophy (Table I).[3 9 11–24] The commonest ocular finding in Lyme disease appears to be conjunctivitis. Steere *et al* in a study of 314 patients with erythema chronicum migrans noted conjunctivitis in 35 (11%), photophobia in 19 (6%), and periorbital oedema in 10 (3%).[3] Unfortunately the authors did not elaborate further. By inference and from our anecdotal experience conjunctivitis is not very prominent in this disease and is short-lived.

Neurological complications in Lyme disease occur in approximately 10% of cases, and over half of patients with them have cranial nerve palsies, most commonly involving the seventh nerve.[12] Oculomotor weakness is infrequent, but may be due to cranial nerve palsy of the III, IV, or VI cranial nerves. Such palsies may occur individually, or in combination with one another and/or with other neurological abnormalities.[12 14] Diplopia is the typical ocular complaint in these instances. Like other neuropathies, oculomotor weakness usually resolves within two weeks to five months after onset.[12 14] Whether antibiotics improve the rate of recovery has not been established.[25] One patient with an Argyll-Robertson pupil[12] and another with a reversible Horner's syndrome[26] have been reported on, and optic atrophy has been noted in several patients (see below).[9 12 27 28]

Papilloedema of diverse causes has been seen occasionally.[12–16 20 22] It has been observed in a minority of Lyme disease patients with meningitis.[14 22] It is then typically bilateral and may be symptomatic, leading to complaints of blurred vision. It is of interest that the intracranial pressure is often not raised, so that the pathogenesis of this condition is obscure. Too few data are available to assess the natural history of papilloedema in Lyme disease meningitis, but antibiotic therapy appears to hasten the resolution of certain other clinical signs.[29] In one report resolution of papilloedema was accompanied by the development of pigment epithelial mottling at the fovea,[16] and in two other cases optic atrophy ensued.[12]

Papilloedema has also been reported in several Lyme disease patients who had increased intracranial pressure but no evidence of meningitis.[15] Sixth nerve palsy was sometimes present in these patients. Cranial tomography failed to reveal mass lesions or enlarged ventricles resulting in a diagnosis of Lyme disease-associated pseudotumor cerebri for some of these patients.[15] Antibiotics plus additional medications for reducing intracranial pressure have been useful therapeutically.

Anecdotal cases of optic neuritis[14 20] and optic atrophy[9 27 28] possibly due to Lyme disease have been reported. Bertuch *et al*[18] described a patient who developed progressive temporal pallor of the right optic disc six months after onset of an illness presumed to be Lyme disease. In addition Shechter[17] described a patient who developed papillitis of the right eye with an inferior altitudinal visual defect three months after the onset of Lyme disease. Despite a course of high dose systemic corticosteroids, the left eye of this patient also became involved. The process eventually stabilised after a course of antibiotics plus corticosteroids. The author's diagnosis in this latter case was ischaemic optic neuropathy due to Lyme disease.

Other late ophthalmic manifestations of Lyme disease have been described. Corneal abnormalities presumed to be due to Lyme disease have been described in four patients who developed a form of interstitial keratitis six months to as long as five years after the diagnosis of Lyme disease.[18 19 21] None of these patients had other symptoms attributable to Lyme disease when the ocular disease was demonstrated, and all four had previously received antibiotic therapy for Lyme disease. The keratitis was characterised by scattered corneal opacities that occurred randomly within the corneal stroma from Bowman's membrane to Descemet's membrane, either unilaterally or bilaterally. Bilateral involvement of the cornea was noted in one case in which the corneal stroma was involved asymmetrically.[19] In one patient minimal neovasculatisation was seen.[19] Two patients were asymptomatic, one of whom was found to have diminished visual acuity on routine school screening; the other two patients complained of decreased vision. The keratitis responded to topical corticosteroids[19 21] but apparently not to systemic or tropical antibiotics,[18] which supports the conjecture that this process has an immunological rather than an infectious origin.

Eye involvement in Lyme disease shares certain similarities with that seen in syphilis. Syphilitic uveitis or iritis occurs in about 4% of patients with secondary syphilis, but may also follow inadequately treated primary syphilis or may be a part of tertiary syphilis.[30] Keratoiritis is the commonest manifestation, but choroiditis, lenticular opacities, retinitis, and panophthalmitis may occur.[30] The vitreous often shows multiple yellow-grey exudates, which tend to spread along retinal vessels.[31] An important differentiating feature of syphilitic keratitis from that so far reported in Lyme disease is the early and massive neovascularisation of the cornea in syphilis.[19]

Most authors suggest treatment of ocular syphilis with high-dose intravenous penicillin, sometimes accompanied by systemic corticosteroids.[31 32] However, steroids alone may be permissive to the spirochaete and are likely to worsen the condition.[31] Similarly, steroids may have contributed to the marked severity of the ocular infection in our patient.

Lyme disease is an emerging infectious disease which may cause eye lesions requiring treatment. Ophthalmologists caring for patients from endemic areas need to be aware of its protean clinical manifestations.

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# Inhibition of microvascular endothelial cell proliferation by vitreous following retinal scatter photocoagulation

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**Abstract**

**Laser photocoagulation of pig retina induced breakdown of the blood-retinal barrier, with the appearance of serum proteins in the vitreous as determined by sodium dodecyl sulphate/polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting techniques. Vitreous from lasered eyes inhibited the proliferation of cultured retinal microvascular endothelial cells in comparison with vitreous from non-lasered control eyes, and the inhibitory effect in the lasered eyes persisted for at least seven days. Inhibition was specific for endothelial cells, since no effect was observed when retinal pericytes or Tenon's fibroblasts were the target cells. These results suggest that indirect scatter photocoagulation may induce regression of neovascularisation by causing breakdown of the blood-retinal barrier and thus releasing into the vitreous serum components which result in inhibition of retinal microvascular endothelial cell growth.**

Preretinal neovascularisation is responsible for many of the blinding sequelae of diabetic retinopathy. Neovascularisation occurs in response to ischaemic damage to inner retinal tissue and is thought to be mediated via diffusible angiogenic factor(s).[1] Panretinal photocoagulation induces regression of the new vessels[2] and has become an established primary therapy for preretinal neovascularisation.

The exact mechanism of regression of neovascularisation is unknown, but a number of hypotheses have been advanced to explain this effect. They include a proposed reduction in angiogenic factor release from ischaemic retina owing to destruction of retinal tissue,[3] to increased availability of oxygen through thinned outer retina,[4] or to disruption of the outer blood-retinal barrier facilitating outward diffusion of the angiogenic factor into the choroid.[5] Recently, on the basis of tissue culture experiments, it has been suggested that the retinal pigment epithelium (RPE) may produce a factor capable of inhibiting the proliferation of vascular endothelial cells.[6] However, RPE cells can also produce retinal vascular mitogens.[7]

In order to study the mechanisms underlying photocoagulation induced regression of neovascularisation we undertook scatter laser photocoagulation of pig retina and examined the properties of vitreous from lasered and unlasered eyes.[8] Our initial study showed that vitreous from eyes which had received laser photocoagulation significantly inhibited the proliferation of retinal microvascular endothelial cells in vitro compared with vitreous from unlasered eyes. These results suggested that an inhibitor of angiogenesis is released from the retina after photocoagulation and diffuses into the vitreous, where it acts directly on preretinal new vessels. In the present study, we have extended this work to an analysis of vitreous proteins, and our results indicate that the major change in vitreous content following laser therapy is an influx of serum proteins and other components, the net effect of which is growth inhibitory activity specifically directed towards endothelial cells.

## Materials and methods

### PHOTOCOAGULATION

Eight 1-year-old miniature pigs received scatter photocoagulation by an argon blue-green laser (HGM Model 5, Litechnica) according to the following protocol. After premedication with 10 mg/kg intramuscular ketamine 10 mg/kg methoxitone was administered intravenously to induce anaesthesia prior to intubation. Anaesthesia was maintained with spontaneous inhalation of a 30% $O_2$/70% $N_2O$ mixture supplemented by 1·5% halothane. The animal's head was positioned on a slit-lamp and one thousand 500 μm laser burns at 300 mW and 100 ms duration were applied to the retina of the right eye through a Goldmann fundus contact lens. The left eye was not lasered and served as the control for each animal. Following photocoagulation the anaesthetic agents were discontinued, and the animals recovered.

### PREPARATION OF VITREOUS

Five of the animals were killed four days after photocoagulation and three after seven days. In each instance the animals were anaesthetised as described earlier and both eyes were enucleated. A blood sample was also taken from some of the animals, and the serum was separated and stored. The animals were killed by intravenous potassium chloride. The globes were immediately dissected and the vitreous was removed and stored at −70°C. Before use the vitreous was thawed, liquefied by an ultrasonicator (MSE Soniprep 150), and finally filter sterilised through a 0·22 μm filter (Millipore, USA).

### CELL CULTURE

Human eyes of variable age and with no known ophthalmic disease were obtained from Moorfields Hospital Eye Bank, London, after corneal

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buttons had been removed. Bovine eyes were collected from a local abattoir. Human RPE cells were isolated and cultured as previously described.[9] Bovine retinal microvascular endothelial cells were grown in a 1:1 mixture of Dulbecco's modified Eagles medium (DMEM) with 7·5% human platelet-poor plasma and pericyte conditioned medium.[10] Bovine retinal pericytes and bovine Tenon's fibroblasts were routinely grown in DMEM supplemented with 20% fetal calf serum.

Cultures between the second and fifth passage were used for all subsequent studies.

### PRODUCTION OF CONDITIONED MEDIA

Conditioned media were prepared as previously described.[7] In brief, cultures of retinal pericytes and RPE cells were grown to confluence in 25 cm$^2$ flasks (Falcon) and washed twice with Dulbecco's phosphate buffered saline without calcium and magnesium (PBSA). After they had been washed 8 ml of DMEM supplemented with 7·5% human platelet-poor plasma was added to each flask. After incubation for two days the conditioned medium was removed and stored at −20°C.

### PROLIFERATION ASSAYS

$2\times10^4$ retinal microvascular endothelial cells were seeded into each gelatinised well of 24-well plates (Flow) in DMEM supplemented with 7·5% human platelet-poor plasma. After a period of two days to allow for attachment and initial proliferation the medium was removed, and the cells were washed twice with plasma-free DMEM. Each well then received 1 ml of one of the following test media:

(1) A 1:1 mixture of DMEM+7·5% plasma and pericyte conditioned medium to which was added 75 μl liquefied vitreous (either 'lasered' or 'non-lasered') or 75 μl PBSA as a control.

(2) A 1:1 mixture of DMEM+7·5% plasma and RPE conditioned medium to which was added 75 μl liquefied vitreous (either 'lasered' or 'non-lasered') or 75 μl PBSA as a control.

After two days in test media the cell numbers were determined by means of a haemocytometer. Each experiment was performed on at least two separate occasions.

Representative vitreous samples were also examined for their effect on pericyte and fibroblast proliferation. $2\times10^4$ cells were seeded in each well of uncoated 24-well plates as described above and incubated overnight to allow for attachment and proliferation. The test media (DMEM+7·5% plasma mixed 1:1 with pericyte conditioned media) plus 75 ml/l of either vitreous or saline were added and cell numbers were determined at two days in the case of fibroblasts and at five days for pericytes, since the latter grew comparatively slowly.

Aliquots of cells from each test were stained with trypan blue in order to determine a cytoxic effect. Each experiment was performed on at least two separate occasions.

### MIGRATION ASSAYS

Migration assays were undertaken as described by Hackett and Campochiaro using 48-well modified Boyden chambers.[11] Briefly the lower wells were filled with test media consisting of 75 ml/l of vitreous added to either DMEM with no serum or DMEM with 7·5% fetal calf serum. Each test medium type was added to eight wells. Control wells had the vitreous substituted with an equivalent volume of PBSA. The wells were then overlaid with a type 1 collagen (Ethicon) coated polycarbonate membrane with 10 μm pores and the chambers assembled. Upper wells were filled with a suspension of one of the cell types to be tested (endothelial cells, pericytes, RPE, or fibroblasts) in serum free medium at a density of $9\times10^5$ cells/ml. The chambers were then incubated for six hours at 37°C. The filter was removed, fixed in methyl alcohol, and stained with modified Wright's stain. The number of cells which had migrated through the polycarbonate filter were counted after the non-migrating cells had been wiped from the top surface. Cell nuclei in 10 high power fields were counted in each well.

### GEL ELECTROPHORESIS

Samples of vitreous (1 μl) were analysed by SDS-PAGE in an 8–25% gradient gel by the Pharmacia Phast System according to the manufacturer's instructions. Samples were run under reducing and non-reducing conditions (with or without mercaptoethanol in the sample buffer).

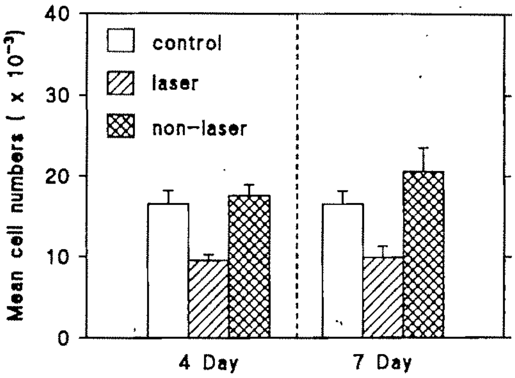

*Figure 1: Effect of 'lasered' and 'non-lasered' vitreous samples (4 and 7 days post treatment) on the proliferation of retinal microvascular endothelial cells in the presence of pericyte conditioned medium. The control consisted of a 1:1 mixture of DMEM+7·5% plasma and pericyte conditioned media to which was added 75 μl PBSA. In the test wells PBSA was substituted with 75 μl of vitreous (laser or non-laser). The vertical bars represent SD.*

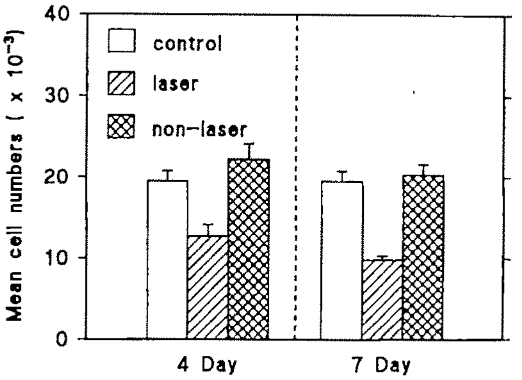

*Figure 2: Effect of 'lasered' and 'non-lasered' vitreous samples (4 and 7 days post treatment) on the proliferation of retinal microvascular endothelial cells in the presence of RPE conditioned medium. The control consisted of a 1:1 mixture of DMEM+7·5% plasma and RPE conditioned media to which was added 75 μl PBSA. In the test wells PBSA was substituted by 75 μl of vitreous (laser or non-laser). The vertical bars represent SD.*

In addition, native polyacrylamide gel electrophoresis of vitreous samples was performed. Gels were double stained with silver nitrate and Coomassie blue dye. Alternatively, proteins separated on the gels were transferred by diffusion blotting in the Pharmacia Phast System on to nitrocellulose membranes and detected with antisera against whole pig serum by the immunoperoxidase procedure according to the manufacturer's instructions. Samples of pig serum and haemolysed pig serum were run on the same gels for comparison.

### STATISTICS

All data from the proliferation and migration assays were expressed as the mean together with standard deviation of the mean. The statistical significance of vitreous related changes was examined by analysis of variance.

## Results

### PROLIFERATION ASSAYS

Vitreous from all laser treated eyes significantly inhibited the proliferation of retinal microvascular endothelial cells in the presence of both pericyte and RPE conditioned media when compared with controls containing PBSA ($p<0{\cdot}001$) (Figs 1 and 2). In contrast, vitreous from unlasered eyes did not significantly affect endothelial cell proliferation ($p>0{\cdot}8$). There was no apparent difference in the degree of inhibition between laser exposed samples from four- and seven-day post-treatment animals in either the presence of pericyte conditioned medium or RPE conditioned medium.

The inhibition of proliferation by vitreous from laser treated eyes appeared to be specific for retinal microvascular endothelial cells, since inhibition was not seen with either retinal pericytes or fibroblasts (Table I).

TABLE I *The effect of vitreous from lasered and non-lasered eyes (four days after treatment) on the proliferation of pericytes and fibroblasts in DMEM+7·5% plasma mixed 1:1 with pericyte conditioned medium. Mean values of six individual wells were made for each test medium. The numbers in parentheses are SD*

| | *Mean number of cells* ($\times 10^{-3}$) | | |
|---|---|---|---|
| *Cell type* | *Control* | *Lasered* | *Non-lasered* |
| Pericyte | 38 (2·2) | 39 (2·1) | 39 (2·5) |
| Fibroblast | 43 (2·6) | 43 (1·9) | 44 (3·0) |

TABLE II *Effect of vitreous from lasered and non-lasered eyes on the migration of retinal microvascular endothelial cells*

| | *No. of cells migrated* | |
|---|---|---|
| *Test media* | *Four days post laser* | *Seven days post laser* |
| DMEM/O+ | | |
| PBSA | 5·2 (1·4) | 6·6 (2·0) |
| Lasered vitreous | 5·5 (1·9) | 6·9 (1·5) |
| Non-lasered vitreous | 5·0 (1·5) | 7·1 (1·7) |
| DMEM/7·5+ | | |
| PBSA | 35·7 (4·4) | 39·0 (4·6) |
| Lasered vitreous | 37·9 (4·6) | 41·8 (5·7) |
| Non-lasered vitreous | 35·7 (6·3) | 40·6 (5·1) |

DMEM/0 indicates serum-free DMEM and DMEM/7·5 indicates DMEM supplemented with 7·5% fetal calf serum. The figures represent the average number of migrated cell in 10 high power fields for each test medium and the numbers in parentheses are the SD.

Trypan blue exclusion techniques did not demonstrate any cytoxic effect by any of the vitreous samples on the cells during the test period.

### MIGRATION ASSAYS

The vitreous from either lasered or non-lasered eyes showed no apparent effect on the migration of either endothelial cells, pericytes, RPE, or fibroblasts in comparison with appropriate controls (Table II).

### GEL ELECTROPHORESIS

In analysis by gel electrophoresis samples of vitreous from untreated eyes showed a small number of protein bands, as predicted for normal vitreous proteins (Fig 3). Samples from laser treated eyes showed a large increase in protein concentration, whose electrophoretic pattern was closely similar to that of pig serum (Fig 3). Immunoblotting of the proteins with

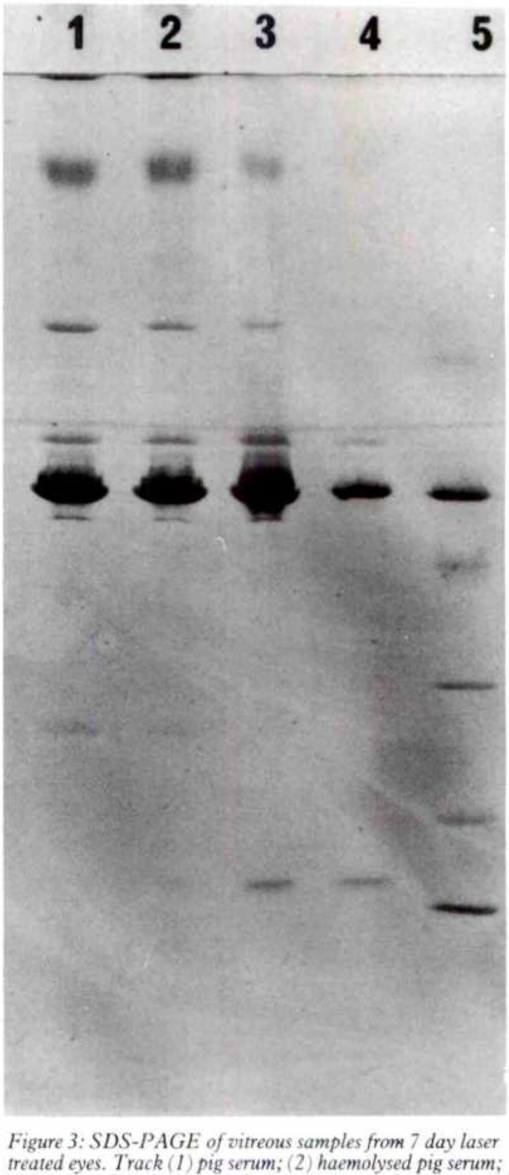

*Figure 3: SDS-PAGE of vitreous samples from 7 day laser treated eyes. Track (1) pig serum; (2) haemolysed pig serum; (3) vitreous from laser treated pig; (4) vitreous from untreated pig; (5) molecular weight markers.*

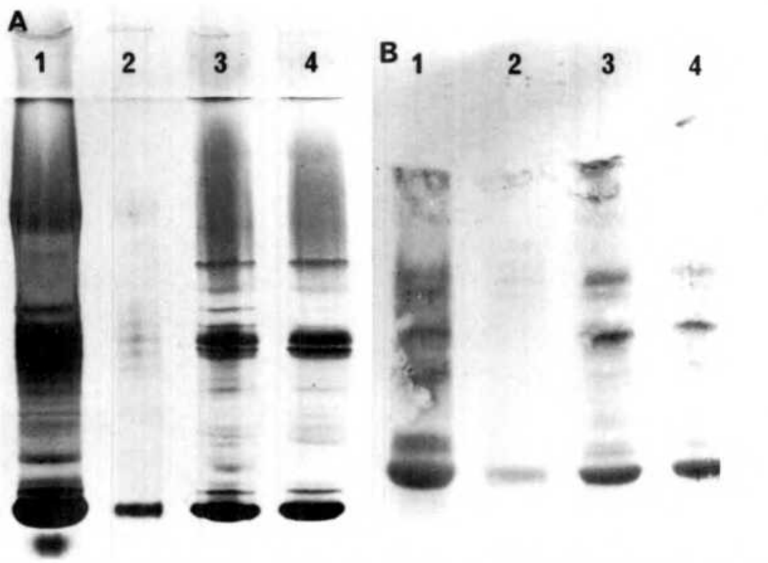

*Figure 4: A: Native PAGE of vitreous samples from 7 day laser treated eyes. Track (1) vitreous from laser treated animal; (2) control vitreous from untreated animal; (3) pig serum; (4) haemolysed pig serum. B: Corresponding nitrocellulose immunoblot of samples, stained with rabbit anti-whole pig serum, with goat anti-rabbit as the second antibody.*

antisera to whole pig serum confirmed that all additional proteins in laser treated vitreous samples were derived from serum (Fig 4). All laser treated samples from four- and seven-day post-treatment animals showed identical patterns with equivalent concentrations of individual proteins (Fig 5).

## Discussion

We have confirmed our previous observation[8] that following panretinal photocoagulation a diffusible factor(s) which inhibits microvascular cell proliferation appears to accumulate in the vitreous. The inhibitory effect was present at both four and seven days after laser treatment. These time periods were chosen because clinical regression of neovascularisation is usually evident during this period following panretinal photocoagulation.[2] Owing to the limited quantity of vitreous available it was only possible to (*a*) use one concentration of vitreous (75 ml vitreous/l of medium was chosen arbitrarily), and (*b*) test the effect of 'lasered' vitreous on the response of microvascular endothelial cells to two mitogenic stimuli. We chose pericyte conditioned medium because pericytes are (*a*) closely associated with retinal capillaries,[12] (*b*) implicated in new vessel formation,[11] and (*c*) capable of producing culture medium which is mitogenic for retinal microvascular endothelial cells.[10] RPE conditioned medium was used because destruction of RPE cells after scatter photocoagulation results in regression of extraretinal neovascularisation,[2] and RPE cells produce retinal vascular mitogens in vitro.[7] Since no significant differences were observed in the degree of inhibition in the presence of either conditioned media, it is likely that the 'lasered' vitreous acted via the same mechanism in both media.

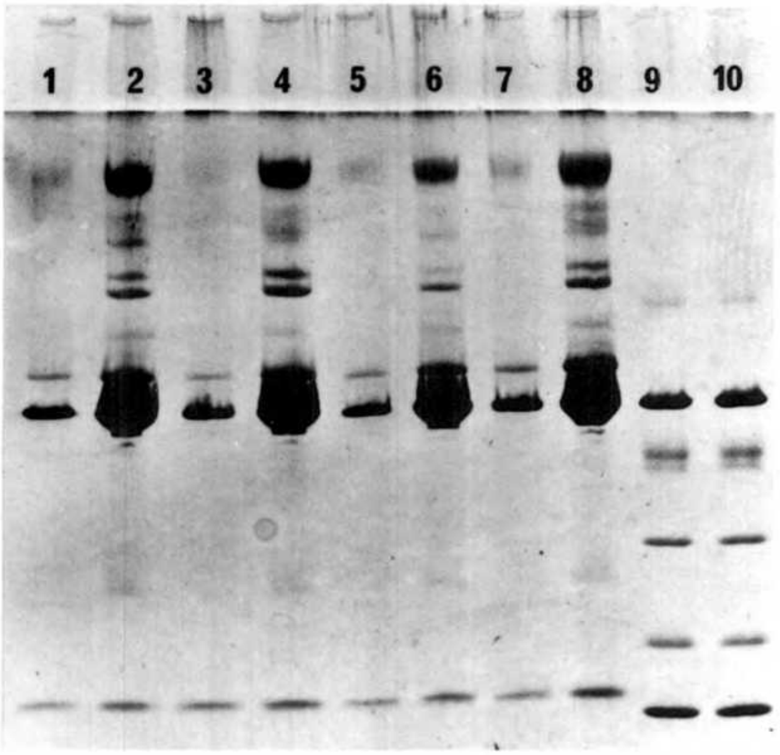

*Figure 5: SDS-PAGE of vitreous samples from 4 day and 7 day laser treated eyes. Tracks 1, 3, 5, 7: control vitreous from untreated right eyes. Tracks 2, 4: vitreous samples from pig 1 and pig 2, 4 day laser treated eyes. Tracks 6, 8: vitreous samples from pig 3 and pig 4, 7 day laser treated eyes. Tracks 9, 10: molecular weight markers.*

The inhibitory effect of vitreous from lasered eyes was specific for retinal capillary endothelial cells, since we observed no inhibitory effect on the proliferation of pericytes or fibroblasts in the presence of pericyte conditioned media. Since both pericytes and fibroblasts have previously been shown to respond to mitogenic factors in pericyte conditioned medium (Wong, unpublished) the results suggest that the mitogens which are responsible for endothelial cell proliferation are different from those for the other cell types studied.

Since the migration of retinal microvascular cells is as important as proliferation in new vessel formation,[14] we examined the effect of lasered vitreous on the migration of retinal endothelial cells. Owing to the limited quantity of material available it was possible to examine the effect of vitreous only on serum induced migration. Thus, although vitreous had no effect on the migration of endothelial cells in the presence of serum, there may be an effect in the presence of conditioned media.

The nature of the laser induced inhibition of endothelial cell proliferation is obscure. Previously it has been suggested that RPE cells release an inhibitor of neovascularisation after laser injury,[6] but RPE cells also release mitogens for endothelial cells,[7] and clearly the role of RPE cells in this system is complex. Both xenon and laser photocoagulation cause damage to the outer blood-retinal barrier,[5,15] and protein concentrations in the vitreous are known to be raised after laser treatment.[15] While some of these proteins were acknowledged to have been derived from serum, it was also suggested by Campochiaro and colleagues that a contribution was derived from damaged retinal cells, in particular the RPE.[15] In the present study we have shown that the great majority of the proteins in the vitreous after laser therapy are derived from serum and that serum proteins persist in the vitreous for at least seven days following laser treatment.

Serum is known to contain inhibitors of endothelial cell proliferation such as transforming growth factor β (derived from platelets)[16] and other inhibitors such as plasminogen activator inhibitor-1, though at very low levels.[17] However, for such a breakdown of the RPE blood-retinal barrier to cause regression of neovascularisation the effect must be in some way 'selective', since leakage of serum proteins into the vitreous is a characteristic of new vessels. The consequence of this breakdown for retinal endothelial cells probably involves an interaction of extravasated serum components with local retinal and/or vitreous components, resulting in either loss of stimulatory activity or production of inhibitory activity. This effect may be quantitative or cumulative over a long time. Our attention should be directed towards identification and characterisation of these serum factors.

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# Blindness and eye disease in Kenya: ocular status survey results from the Kenya Rural Blindness Prevention Project

Randolph Whitfield, Larry Schwab, Dennis Ross-Degnan, Paul Steinkuller, Jack Swartwood

**Abstract**

**A series of eight regional eye surveys were conducted in Kenya as part of the Kenya Rural Blindness Prevention Project. Each survey consisted of clinical examinations of about 1800 individuals selected by a random cluster sampling technique in geographically distinct and culturally homogeneous rural areas; 13 803 examinations were completed in all. Together these surveys provide the basis for national estimates of the prevalence and aetiology of visual loss and ocular pathology. The results showed that 0·7% of rural Kenyans are blind in the better eye by WHO standards, and another 2·5% suffer significant visual impairment. Rates of visual loss tend to increase five-fold in each 20-year age cohort. Females have higher prevalence of visual loss than males over age 20, and certain geographical areas have markedly higher rates. The commonest cause of both blindness and visual impairment is cataract, accounting for 38% of all visual loss. Trachoma (a localised problem), glaucoma, macular degeneration, and severe refractive errors follow cataract as leading causes of blindness in the better eye. Trauma, corneal scars of various causes, phthisis, and staphyloma are important causes of monocular blindness. Nutritional eye disease does not appear to be a problem of any magnitude in rural Kenya.**

Preventable blindness has long been identified as a global public health problem.[1 2] Approximately 28 million people are blind worldwide and over two-thirds of them live in developing nations.[3] Often blindness rates in poor countries are 10 to 20 times those in industrialised nations,[4] and in certain communities with particular disease problems like onchocerciasis or severe trachoma as much as 30–50% of the population may be affected, especially among the elderly. This occurs not only because of limited access to health services, but also because of environmental or climatic stresses, poor hygiene, and other factors associated with a low standard of living. Approximately 80% of the people who are blind in the developing world suffer from conditions which are avoidable in the sense that their blindness could have been prevented or is surgically correctable.

The true consequences of blindness are difficult to calculate. In addition to the social and psychological isolation of the blind and the stigma attached to their helplessness, in a situation of very limited resources for survival, a blind person can be a tremendous economic burden. The presence of high rates of blindness in a community implies a significant loss of its productivity, not only because the blind often cannot be productively engaged, but also because others must care for them and generate the resources needed for their survival.

The International Eye Foundation (IEF) has assisted the Government of Kenya in developing preventive and therapeutic ophthalmic services since 1972, when an IEF ophthalmologist was posted to a rural provincial hospital as the government eye specialist. Kenya typifies the health manpower situation in many African nations, in that most of the medical facilities, manpower, and resources are concentrated in large cities, especially the capital city. There are only a few government ophthalmologists assigned to rural facilities, concentrating their efforts on the rural population. A pilot ocular survey among the rural Samburu people[5] confirmed that most blindness in rural Kenya is either preventable or curable. For these reasons the underlying rural needs are better addressed by training clinical and surgical personnel who are not ophthalmologists to provide ophthalmic care, and by eye disease prevention programmes, rather than by the isolated clinical efforts of eye specialists.

Substantial funding from the United States Agency for International Development beginning in October 1976 made possible an IEF sponsored Kenya-wide Rural Blindness Prevention Project (KRBPP).[6] The objectives of this project were to strengthen and extend the capabilities of the established system of therapeutic rural eye care, and to divert the emphasis in rural eye care away from a purely therapeutic approach towards prevention of blindness through health education, screening, and treatment at the primary care level, and early referral of people in need of specialised care. To plan for these objectives it was necessary to define accurately the prevalence and causes of blindness among rural Kenyans.

## Material and methods

### SAMPLE DESIGN

Because of constraints in time and resources a national statistical sample of the rural population was not organised. Instead advantage was taken of the fact that tribes in Kenya traditionally live in defined geographical regions and have not tended to intermingle in their rural homes as they have in the cities. Specific rural areas that represented the major population groups, as well as the ranges of ecological conditions that might

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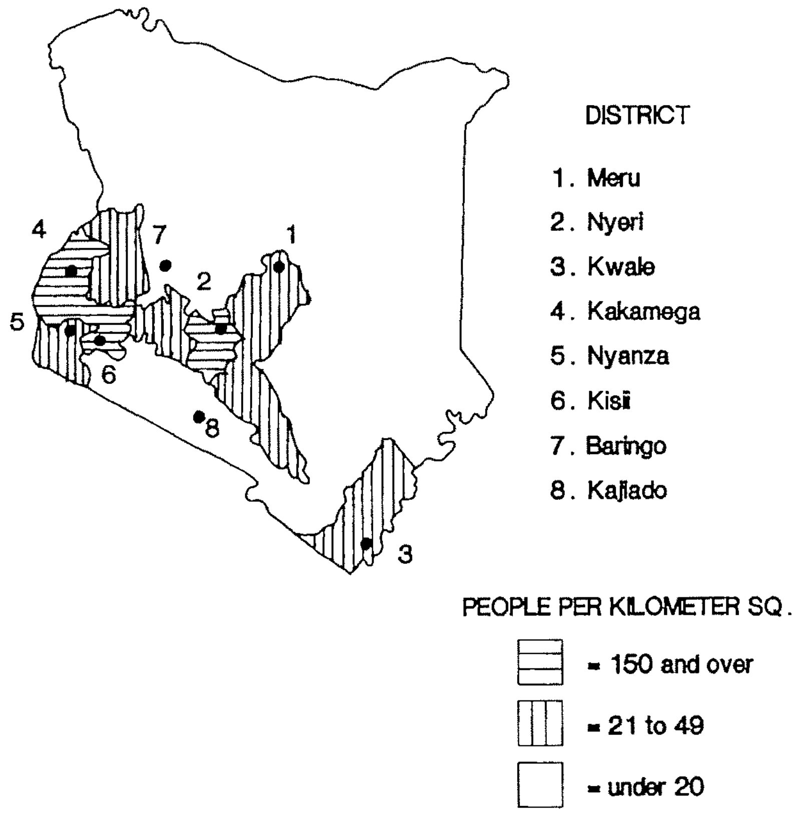


*Figure 1: Kenya eye disease surveys: sample areas and population density.*

impinge on eye disease, were selected to be surveyed. A series of population based eye disease surveys were conducted in eight rural districts of Kenya (Fig 1). National estimates were inferred from these independent district samples by weighting methods described below.

The methodology used to draw the samples for these surveys has been described elsewhere.[7] Briefly, within the district inhabited by a particular group to be surveyed meetings were held with regional and local officials to identify smaller administrative divisions that were typical of the group and the area. A random cluster sample was then drawn from these administrative divisions by means of a sampling frame based on tax lists, land adjudication records, or, in less settled areas, lists of heads of household assembled by local chiefs.

The cluster sample technique used was similar to the one recommended by the World Health Organisation (WHO) for immunisation surveys.[8] Although sample size was sometimes varied to meet particular objectives, each survey was generally planned to consist of 30 clusters of households. Each cluster was begun at a random starting point selected from the sampling frame and was continued by adding all members of the next nearest household until the total number of eligible residents in the cluster exceeded 60. Examinations in each cluster continued until at least 90% of all eligible persons were examined. Thus there were about 1800 people in the typical regional survey, and 13 803 were examined over the course of the eight surveys.

## CLINICAL METHODS

The survey teams consisted at a minimum of an ophthalmologist, an ophthalmic clinical officer or ophthalmic assistant, a registrar, and a locally-hired clerk who was familiar with the survey area and local language. Each survey member was registered, screened for visual acuity, had a history taken by the clinical officer, and was then examined by the ophthalmologist. There were nine separate examiners from the staff of the KRBPP or the Kenya Ministry of Health over the course of the eight surveys, with three primary examiners (RW, LS, PS) involved consistently over the seven years the surveys were conducted.

Each examination was carried out in a centrally located public place or in the homes of survey members, according to a structured clinical protocol. Using a focal handlight, 2× binocular magnifying loupes, and an ophthalmoscope, the ophthalmologist examined the lids, conjunctiva, and cornea of every survey member. In addition, for every survey member with vision less than 6/18 in either eye, and for everyone aged 40 and over, funduscopy was carried out by direct ophthalmoscope, with dilatation of the pupil if necessary. Schiøtz tonometry was performed on all persons aged 40 and over and on anyone below that age when indicated.

The results of examinations were reviewed each evening for accuracy and completeness, and any results about which there were questions were resolved by consensus of the survey ophthalmologists.

*Visual acuity.* With the exception of children unable to understand or co-operate, visual acuity was measured on all survey members with Landholt C-ring optotypes. The procedure was carried out at 6 m in available outdoor light (except in the first survey, when the procedure was performed indoors under incandescent light) with refractive correction by spectacles if available and usually worn. If visual acuity was less than 6/18, it was rechecked with pinhole, and, if there was improvement, this result was recorded as best visual acuity. The visual acuity of infants and children unable to be tested was measured by ability to fix centrally on a moving focal handlight, which was considered to be an adequate indication of normal vision.

Visual acuity was coded according to standard WHO definitions.[9] In this analysis vision less than 6/18 but better than or equal to 3/60 is classified as visual impairment; vision less than 3/60 is classified as blindness; and together these two conditions are referred to as visual loss.

*Diagnosis.* The examining ophthalmologist was required to assign a single principal diagnosis of the reasons for visual loss in each eye with vision less than 6/18. For conditions with multiple causation the examiner assigned the underlying or precipitating cause or the one which accounted for the major component of the visual loss. All reasons for visual loss refer to the cause of the loss in the eye with *better acuity* if vision in the two eyes was unequal, and to the cause in the right eye if both eyes were equally effected.

*Cataract.* Any opacity of the lens visible to the ophthalmologist with direct ophthalmoscopy against the red reflex was classified as a cataract. Cataracts are analysed in three categories depending on whether the eye in which they

TABLE I *Regional survey area characteristics*

| *District* | *Tribal group* | *Sample size* | *Attributed % of rural population* | *Geography* | *Climate and rainfall* | *Economy* |
|---|---|---|---|---|---|---|
| Meru | Meru | 1142 | 16·1 | Nyambene Hills northeast of Mt Kenya runoff, scarce water | Temperate to hot; moderate rain but high subsistence farming | Cultivation of miraa (a plant used as a stimulant) |
| Nyeri | Kikuyu | 1825 | 20·4 | Hilly highlands west of Mt Kenya plentiful | Cool temperate, high rainfall, water | Coffee and tea farming, subsistence farming |
| Kwale | Mijikenda | 1342 | 6·8 | Coastal plain and immediate hinterland | Hot, humid, moderate rainfall | Fishing, subsistence farming, tourism |
| Kakamega | Abaluhya | 1651 | 23·6 | Highland plateau west of Rift Valley reliable water | Temperate to hot, moderate rainfall | Cotton farming, some coffee farming, subsistence farming |
| Nyanza | Luo | 1807 | 11·5 | Basin south of Lake Victoria | Hot, humid, rainfall moderate but variable | Cotton farming, fishing, subsistence farming |
| Kisii | Kisii | 1753 | 6·2 | Hilly plateau west of Rift Valley | Temperate, high rainfall; good water | Tea and coffee farming, subsistence farming |
| Baringo | Tugen<br>Njemps<br>Pokot | 1182<br>581<br>596 | 6·7 | Tugen Hills, Lake Baringo plain, Rift Valley north of lake | Varied; temperate to hot; moderate to very low rainfall | Coffee and subsistence farming; livestock herding in arid areas |
| Kajiado | Masai | 1924 | 8·7 | 1000 m grassland plateau east of Rift Valley | Hot, arid, semidesert; water scarce | Herding cattle, goats |

occur had normal visual acuity, visual impairment, or blindness.

*Trachoma.* This paper reports only the basic findings for visual loss due to trachoma and prevalence of trachoma inflammation. Detailed findings on the disease and related ocular pathology will be reported elsewhere. Visual loss was determined as being due to trachoma in three situations: (1) the simultaneous presence of corneal opacities, and entropion or trichiasis; (2) the presence of focal corneal opacity due to secondary bacterial infection or corneal ulcer where there were other clinical signs of trachoma (active inflammation, scarring of the tarsal conjunctiva, corneal or limbal pannus, or Herbert's pits); (3) the presence of trachomatous keratitis that was believed to affect visual acuity. The scoring of trachoma inflammation was based on recommendations[10] of the WHO and coded by a simplified recording system.

*Refraction.* Formal measurement of the type and severity of refractive errors was not carried out. When refractive error was considered to be a possible cause of visual loss, the presence of refractive error was confirmed by lens power readings from the ophthalmoscope or by observed improvements in acuity with pinhole examination.

*Glaucoma.* Visual field testing could not be performed during these surveys for logistic reasons. In the absence of such a definitive test for diagnosis of glaucoma as a cause of visual loss the survey protocol required observation of one of the following: a pathological optic disc (marked pallor of the nerve head, or vertical cupping greater than 0·5) in the presence of raised intraocular pressure (>21 mmHg); markedly raised intraocular pressure (>26 mmHg) without visualisation of a pathological disc; a history of glaucoma surgery or treatment.

Because of the criteria used for identifying the disease, glaucoma as a cause of visual loss is likely to be underestimated in the surveys, but there is no way of determining the extent to which this occurred. Cases of low-tension glaucoma, and those where adequate assessment of the optic disc was not possible (for example, due to the presence of a cataract), were unlikely to be classified as glaucoma. Furthermore, because tonometry and funduscopy were performed routinely only on persons over 40, early and borderline glaucoma cases in the younger age groups that were not yet suffiiciently advanced to affect central vision also may have been missed.

*Retinal disorders.* Age related macular degeneration and other retinal anomalies were diagnosed on clinical grounds alone, as diagnostic laboratory investigations were not feasible.

## METHODS OF ANALYSIS

Because of the great sensitivity of estimates of the prevalence and causes of visual loss to the distribution of age in a population, a standardisation procedure was carried out to minimise the effects of random differences in the age distribution of the eight regional survey samples. Each survey population was adjusted to the national population age distribution from the 1979 census by weighting age categories according to whether they were over- or undersampled relative to the standard. This procedure allows more appropriate regional comparisons and ensures that national estimates are less influenced by sampling differences.

Because the surveyed regions, and the locations within them, were not selected randomly, there is no unbiased procedure for estimating the true population prevalence of blindness or of other ocular conditions. Within each region, however, an assumption was made that the particular locations from which the sample was randomly drawn were representative of a broader population group, and that estimates of rates from the survey sample would apply to the underlying regional population within reasonable bounds of error.

National estimates were computed by attributing to each regional survey a certain proportion of the national rural population, based on similarity in tribal composition, geography, and climate (Table I). Observations within each survey were appropriately weighted so that the national estimates reported reflect these attributed proportions.

For the reasons mentioned, and also because the sample was drawn in clusters, there is no unbiased procedure for calculating sampling errors or confidence intervals for the estimates. No standard errors are reported, though it would

TABLE II *Visual impairment and blindness by age by sex: percentage by acuity level**

| | *Age group* | | | | *All* |
|---|---|---|---|---|---|
| | *0–19* | *20–39* | *40–59* | *60+* | *Kenya* |
| *Male* | | | | | |
| Normal | 99·7 | 98·5 | 94·3 | 66·6 | 97·3 |
| Impaired | 0·2 | 1·0 | 4·4 | 26·9 | 2·1 |
| Blind | 0·1 | 0·6 | 1·2 | 6·5 | 0·6 |
| Weighted N† | (3925) | (1185) | (510) | (304) | (5925) |
| *Female* | | | | | |
| Normal | 99·7 | 98·0 | 89·7 | 61·4 | 96·4 |
| Impaired | 0·2 | 1·7 | 8·6 | 29·2 | 2·8 |
| Blind | 0·1 | 0·3 | 1·7 | 9·4 | 0·8 |
| Weighted N† | (4178) | (2227) | (932) | (315) | (7653) |

*All categories refer to acuity in the better eye with available correction. Normal=6/18 or better; impaired=worse than 6/18 but better than or equal to 3/60; blind=worse than 3/60.
†Weighted according to the proportion of the national rural population represented by each survey region and after adjusting to a standard age distribution based on all surveys combined.

be possible to compute rough estimates based on assumptions of simple random sampling from the information on sample size presented, and to inflate them by an appropriate factor (perhaps 2–4 times) to account for the non-randomised design and clustering.

## Results

### RATE OF BLINDNESS AND VISUAL IMPAIRMENT

The prevalence of blindness and visual impairment by age and sex group is presented in Table II. About 0·7% of all rural Kenyans were blind in their better eye, and another 2·5% had vision which was substantially impaired. Females exceeded males by slight percentages in both these categories.

As expected, the prevalence of visual loss showed a very strong relationship with age, increasing by approximately a factor of 5 in each 20-year age cohort. In the most severely affected group of rural Kenyans, those over the age of 60, about 1 in 12 were blind, and another 28% suffered from visual impairment. Females had a notably higher prevalence of visual loss over the age of 40, and especially in the 40 to 59 year cohort, where total prevalence was nearly double that of males (10·3% vs 5·6%).

There was a fair degree of consistency in the prevalence of impairment and blindness across all the regions surveyed (Table III), with three exceptions. In the two surveys of pastoral groups, among the Masai in Kajiado and among the Pokot and Njemps in Baringo (not separated in Table III from the non-pastoral groups in Baringo) a markedly higher total prevalence of visual loss was found. However, the highest prevalence of blindness was found in Meru, among a settled agricultural group.

### REASONS FOR VISUAL LOSS

Cataract was the major cause of blindness in rural Kenya, with a prevalence of 2·5 per 1000, accounting for 36% of all blindness (Fig 2). Following cataract in prevalence were trachoma (1·3/1000), glaucoma (0·6/1000), macular degeneration (0·5/1000), and severe refractive errors or amblyopia (0·4/1000). Blindness due to xerophthalmia – nutritional blindness – was estimated to occur at a rate of less than 1 per 10 000 individuals overall in rural Kenya and was not found in any person examined under the age of 20.

Cataracts were also responsible for 39% of all visual impairment (rate of 10·0/1000). It was the most prevalent cause of visual loss in six of the eight survey areas and was second to refractive error in the remaining two (Nyeri and Kisii). Refractive errors and macular degeneration were found to be equally prevalent (4·5/1000) as leading causes for visual impairment after cataract. They were followed in importance by trachoma (3·3/1000) and corneal scars due to causes other than trachoma, trauma, or xerophthalmia (corneal scar/other) (1·2/1000).

The prevalence by age group of the causes of visual impairment (rate of 10·0/1000). It was the Figure 3. Cataract, trachoma, refractive errors, macular degeneration, and glaucoma all show sharp increases in prevalence among those 60 and over, while trachoma and cataract stand out in importance as blinding conditions in the two preceeding decades. The relative prevalence of the leading causes of visual loss was found to be similar for men and women in all age groups, except that visual impairment and blindness due to trachoma occur more frequently among women beginning at age 40.

### PREVALENCE OF OCULAR CONDITIONS

Ocular pathologies have as their most important endpoint the inability to see, and the ensuing blindness is not only a health problem but a major socioeconomic problem as well. From a public health perspective, therefore, the most appropriate way to organise diagnoses obtained through prevalence survey is by conditions which affect both eyes or the eye with better vision. However, from the perspective of making decisions related to training health system personnel about common conditions or of public

TABLE III *Rates of visual impairment and blindness by regional survey: percentage by acuity level**

| | *Regional survey* | | | | | | | | *All* |
|---|---|---|---|---|---|---|---|---|---|
| | *Kakamega* | *Meru* | *Nyeri* | *Kwale* | *Nyanza* | *Kisii* | *Baringo* | *Kajiado* | *Kenya* |
| Normal | 98·5 | 94·5 | 97·6 | 97·4 | 96·8 | 96·9 | 96·9 | 93·3 | 96·8 |
| Impaired | 1·0 | 4·0 | 2·1 | 1·8 | 2·6 | 2·7 | 2·5 | 5·4 | 2·5 |
| Blind | 0·5 | 1·5 | 0·3 | 0·7 | 0·6 | 0·4 | 0·6 | 1·3 | 0·7 |
| Weighted N† | (3174) | (2210) | (2778) | (934) | (1576) | (842) | (902) | (1176) | |

*All categories refer to acuity in the better eye with available correction. Normal=6/18 or better; impaired=worse than 6/18 butbetter than or equal to 3/60; blind=worse than 3/60.
†Weighted according to the proportion of the national rural population represented by each survey region, and after adjusting to a standard age distribution based on all surveys combined.

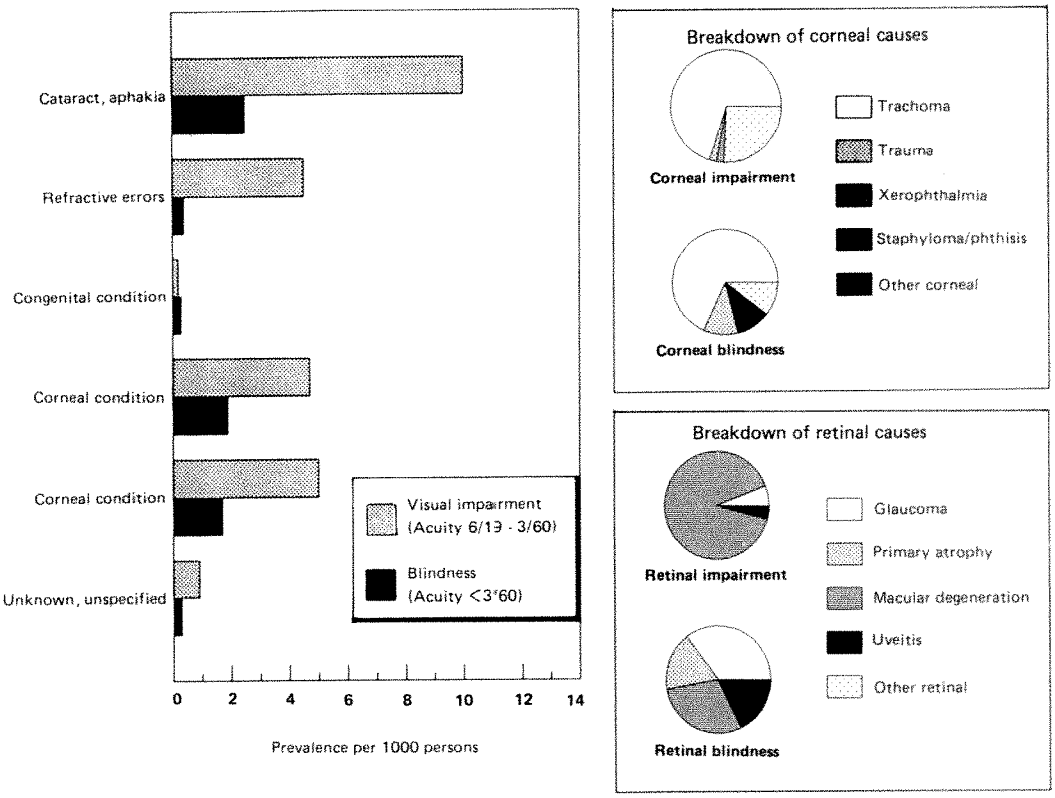


*Figure 2: Conditions causing loss of vision in the eye with better visual acuity*

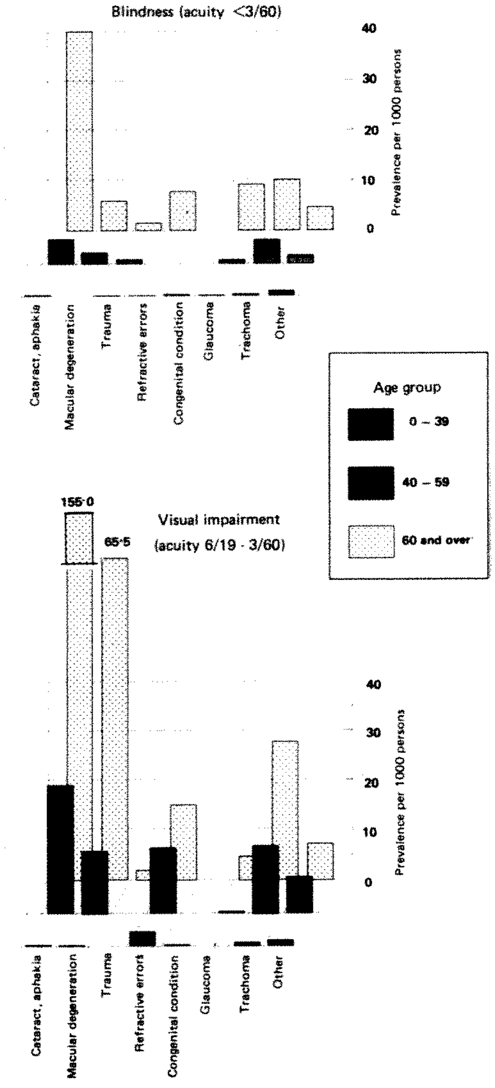


*Figure 3: Reasons for loss of vision by age group.*

health education, it is also useful to examine the prevalence of sight affecting conditions in either eye (Fig 4).

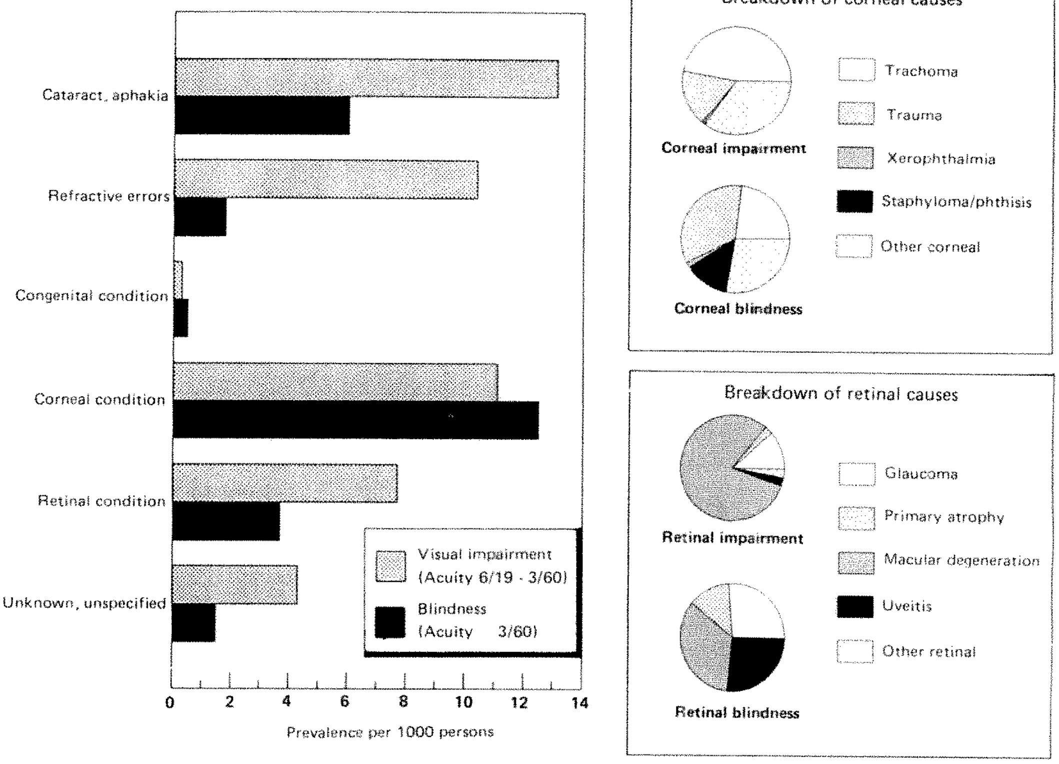
From this perspective cataract is again the major cause of visual loss. Its prevalence as a blinding condition more than doubles (6·0/1000), since many people have at least one eye with a dense cataract even if the other still retained better sight. Trauma, which is most often monocular, assumes a position as the second most prevalent blinding condition (4·3/1000). It is followed in importance by corneal scar due to non-trachomatous infections (3·5/1000) and trachoma (2·9/1000). Phthisis and staphyloma of unknown aetiology (1·7/1000), which are also most often monocular, are nearly equal in prevalence to blinding refractive problems (1·8/1000).

Table IV arrays the prevalence by age group of the most important ocular diseases and conditions from a public health standpoint. Inflammatory trachoma is the most prevalent ocular disease in rural Kenya, with 18·7% of the entire population, and about 1 in 4 children under the age of 10, affected overall. The prevalence in all age groups, but especially among children, varied dramatically among survey areas. Over 80% of those under the age of 10 had active trachoma in Meru and Kajiado; about 50% had active disease among the Pokot in Baringo; 25% in Nyeri and among the Njemps in Baringo; 10% among the Tugen in Baringo; and less than 1% in the remaining survey regions.

The prevalence of visual loss due to sequelae of trachoma varied among survey areas even more sharply – 1·6% of the population in Meru, 1·4% among the affected groups in Baringo, 1·0% in Kajiado, 0·2% in Nyeri, and none in the remaining areas.

There is a very low prevalence of signs of

*Figure 4: Conditions causing loss of vision in any eye examined.*



potential nutritional eye disease in rural Kenya, especially among children under 5, who are at the highest risk of a nutritional crisis which might precipitate vitamin A deficiency. No cases of corneal xerosis or active keratomalacia, the two least equivocal signs of current vitamin A deficiency, were found in any of the surveys. Like trachoma, the occurrence of nutritional eye disease appears very localised. Nine of the 10 cases of visual loss due to old xerophthalmia were found in the Baringo survey, and the other was among the Masai in Kajiado.

TABLE IV *Selected ocular conditions by age: percentage with condition in either eye*

| | *Age group* | | |
|---|---|---|---|
| | *0–39* | *40–59* | *60+* |
| Lens opacities: | | | |
| With visual acuity >6/18* | 0·1 | 2·3 | 10·8 |
| With visual loss or aphakia | 0·1 | 6·1 | 32·1 |
| Weighted N | (10439) | (1390) | (609) |
| Corneal and globe conditions: | | | |
| Ulcer of any origin | 0·3 | 0·4 | 0·2 |
| Dystrophy or degeneration | 0·2 | 2·1 | 7·1 |
| Nebula, macula, or leucoma | 2·2 | 5·8 | 11·2 |
| Phthisis | 0·2 | 0·8 | 1·9 |
| Staphyloma | 0·1 | 0·3 | 0·5 |
| Weighted N | (11600) | (1449) | (628) |
| Disorders of the optic nerve head or macula: | | | |
| Glaucomatous cupping | NA† | 1·1 | 2·8 |
| Optic disk pallor | NA | 0·7 | 1·3 |
| Optic atrophy | NA | 0·6 | 1·2 |
| Macular degeneration | NA | 3·0 | 13·9 |
| Other macular lesions | NA | 1·0 | 10·5 |
| Pigmentary degeneration | NA | 0·1 | 0·6 |
| Other retinal lesion | NA | 1·5 | 8·6 |
| Weighted N | (–) | (1360) | (568) |
| Schiotz intraocular pressure: | | | |
| 22–25 mm | NA | 2·2 | 3·1 |
| 26+ mm | NA | 1·5 | 3·8 |
| Weighted N | (–) | (957) | (535) |

| | Age group | | | |
|---|---|---|---|---|
| | 0–4 | 5–9 | 10–19 | 20+ |
| Potential nutritional eye disease: | | | | |
| Bitot's spots | 0·1 | 0·6 | 0·3 | 0·2 |
| Conjunctival xerosis | <0·1 | 0·3 | 0·1 | 0·1 |
| Leucoma from keratomalacia‡ | <0·1 | <0·1 | <0·1 | <0·1 |
| Conjunctival inflammations: | | | | |
| Inflammatory trachoma | 27·1 | 23·8 | 16·6 | 14·0 |
| Purulent conjunctivitis | 3·1 | 1·3 | 0·2 | 0·4 |
| Tarsal or limbal vernal | 0·1 | 0·2 | 0·4 | 0·3 |
| Weighted N | (2541) | (2223) | (3415) | (5843) |

*An individual with cataracts of both types is counted in both categories.
†Ophthalmoscopy and intraocular pressure examination performed only if indicated on persons under 40.
‡No cases of corneal xerosis or active current keratomalacia were found.

Glaucomatous cupping was found in 1·1% of the rural population between 40 and 59 years and in 2·8% of those over 60. In addition optic disc pallor or atrophy of the optic nerve, either one of which might indicate the presence of glaucoma, was found in an additional 1·3% of the 40–59-year group and in another 2·5% of those over 60. A raised intraocular pressure (over 21 mmHg) on Schiøtz tonometry, which may indicate open-angle glaucoma, was found in 3·7% of those between 40 and 59 and 7·0% of those over 60, and about half of these individuals were found to have very high (over 26 mmHg) pressures.

## Discussion

A substantial part of the Kenyan rural population, particularly in older people, has been shown to suffer from blinding or visually impairing eye disease. However, without a standard of comparison it is difficult to evaluate the severity of the problem. Relevant population estimates of a similar nature to this one are scarce.

It has been estimated that the prevalence of blindness in the United States is 0·2%,[11] but this is based on a more liberal criterion for blindness (visual acuity equal to or less than 6/60). Although it is impossible to give an exact comparison with this figure because of the way in which acuities were recorded in this series of surveys, it can be estimated that approximately 1·7% of rural Kenyans would have been blind by this standard, a figure 8·5 times as large as the rate in the USA.

There have been two major recent population based national surveys of eye disease in developing countries, both of which used the same WHO criterion for blindness employed in this study. In Nepal the Ministry of Health/WHO[12] reported a prevalence of 0·9% for blindness and 1·9% for visual impairment. In Saudi Arabia Tabbara and Ross-Degnan[13] reported comparable figures of 1·5% blind and 7·7% visually impaired. In addition to these national studies Chirambo *et al*[14] reported a blindness prevalence of 1·3% in the Lower Shire Valley of Malawi. Rural Kenya, with an estimated 0·7% blind and 2·5% impaired, is therefore quite similar overall to Nepal and much less severely affected than Saudi Arabia. However, the two worst regions in the Kenyan series – Meru and Kajiado – have similar prevalences of blindness to those found nationally in Saudi Arabia, and one might suggest that 1·5% is typical of moderate to severe trachoma environments in the developing world.

It is not surprising that cataract was the leading cause of visual impairment and blindness in rural Kenya. The WHO reports that it is the leading cause of blindness worldwide,[3] despite the fact that it is no longer a leading cause in industrialised nations. Given the primacy of cataract as a cause of visual loss, it is readily seen that the major thrust of any blindness prevention programme in an environment like Kenya should be directed at cataract. Because the supply of ophthalmologists in African countries is typically very limited, cataract programmes are often most productive when they rely on non-ophthalmologists trained to perform simplified cataract extractions by a standardised surgical technique.[15]

Trachoma was the second leading cause of blindness overall in rural Kenya, but the prevalence of both current inflammation and blinding sequelae varied widely among the survey areas. A variety of factors may be responsible for this variability, yet it is impossible to separate their independent effects because of their tendency to vary together in the areas studied.

High in importance in the natural history of blindness from trachoma would certainly be access to adequate supplies of water, since the disease is easily controlled with adequate personal hygiene. People surveyed who live in arid areas of rural Kenya – the Masai in Kajiado and the Pokot and Njemps in Baringo – tended to have a higher prevalence of trachoma in all its manifestations. However, the first two tribes, and to a certain extent the third, also rely on the herding of livestock for economic livelihood and live in quite close proximity to their animals. They are therefore exposed to an additional risk factor, the persistent eye seeking flies which have been implicated in the spread of the disease.

Visual loss due to trachoma occurred with highest prevalence not among these arid area groups, however, but among the Meru. These people live in an area with rainfall adequate for agriculture, but with porous volcanic soil that absorbs water rapidly, passing it directly down to a deep water table. This makes access to daily supplies of water for hygiene a problem. However, trachoma inflammation and blindness were also found in Nyeri, where people enjoy quite good rainfall, ready access to water and to medical services, and a relatively high level of socioeconomic development for rural Kenya. But trachoma was not found among other rural tribes living in similar circumstances. One must conclude that in Nyeri, and to a certain extent in Meru, it is the cultural pattern of hygiene that is a major factor in the continuing presence of the disease.

In addition to trachoma and cataract many of the other leading causes of visual loss in rural Kenya are preventable or curable. Some conditions are most appropriately addressed by increasing access to prompt and effective treatment by primary care personnel throughout the health system. Much of the visual disability due to trauma and other corneal lesions could be prevented in this manner. In addition, most visual impairment from refractive errors could be alleviated by access to optometric services and spectacles.

A more difficult preventable problem, and an extremely important one given its status as third leading cause of blindness, is that of glaucoma. For the same reasons that open-angle glaucoma is underdiagnosed in field surveys it tends to go unnoticed in the general population. The onset of visual loss from glaucoma is typically slow and insidious, and clinical signs are difficult to recognise and identify reliably. Generally neither the clinical signs nor loss of central visual acuity are apparent until late in the course of the disease.

The best available prevalence estimate for glaucoma in a white population, from the Framingham Eye Study,[16] is 1·9% in people aged 52 and older, an estimate based on very detailed visual field examinations. The comparable group in this age cohort in rural Kenya has a prevalence of 2·1% with visible pathologically cupped optic disc and raised IOP, which represents an extremely conservative estimate of the prevalence of glaucoma disease in all its stages.

One can conclude that glaucoma is probably considerably more prevalent in the Kenyan rural population than in Caucasian populations of industrialised nations, and that it represents a major class of preventable blindness for which there is not yet any clearly defined strategy for diagnosis and treatment. More detailed research on its true prevalence and on the relative efficacy of methods of screening and treatment is clearly indicated.

In summary, blindness and visual impairment have been shown to be much commoner in rural Kenya than in industralised countries. However, except for certain subgroups, rates of visual disability are lower than those found in the Middle East. The prevalence or visual loss rises sharply with increasing age, and females have a higher prevalence of visual loss than males, especially due to trachoma. Except for age related macular degeneration, the major causes of blindness – cataract, trachoma, glaucoma, refraction, and other corneal opacities – are either preventable or curable.

This work was completed with the co-operation, material, and financial assistance of the Government of Kenya, the United States Agency for International Development, the World Health Organisation Programme for the Prevention of Blindness, the Kenya Society for the Blind, institutional and private donors to the International Eye Foundation, the many dedicated people who worked in these surveys, and the people of rural Kenya. It is dedicated to the memory of the late Dr John Harry King Jr, the founder of the International Eye Foundation.

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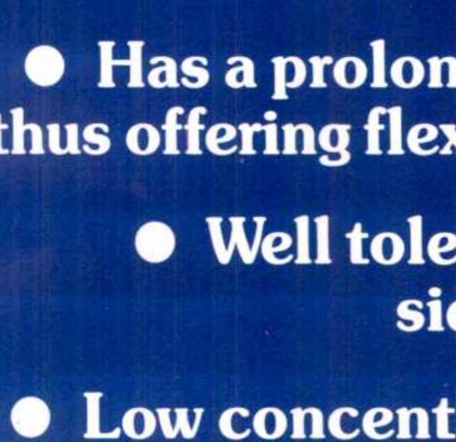

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# 3.8 Million blinded by cataract each year: projections from the first epidemiological study of incidence of cataract blindness in India

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## Abstract

**Data from a population based longitudinal study of randomly selected communities in Central India have for the first time provided direct estimates of age specific incidence of blindness from cataract. Person-time denominators have been used to compute age specific incidence rates (risk) of blindness from cataract for populations aged 35 and older. These age specific incidence measures have been applied to the 'population at risk' in each 5-year age class in order to estimate the total number of new cases of cataract blindness that occur in the country each year. The findings indicate that an estimated 3.8 million persons become blind from cataract each year in India (approximate 95% confidence limits: 3 to 4·5 million). The reasons why the estimates are considered as minima, and their implications concerning future national planning of ophthalmic services, are briefly discussed.**

During the past decade a number of cross-sectional surveys have provided data on prevalence (existing cases) of cataract and of blindness due to cataract in various parts of the world.[1-5] These data indicate that cataract is by far the commonest cause of blindness and visual disability worldwide. However, these prevalence data provide useful information on only the backlog of the cataract problem and do not give information on the number of new cases that occur each year. The latter incidence information is an important prerequisite to rational long-term planning of basic ophthalmic services on a regional or national scale. This paper reports the findings of the first population based longitudinal study which was designed to provide a direct measure of incidence (new cases) of cataract blindness and to evaluate certain risk factors.

## Material and methods

The collaborative study was started in 1982 and was conducted in the Arang Block of Raipur District in Central India. The baseline data were collected from a random sample of 19 communities in the Arang Block (population *c*. 100 000). The sample included 1735 persons aged 30 and older. These constituted the study cohort. Examinations and interviews were carried out by an ophthalmologist and an ophthalmic epidemiologist with the help of three specially trained ophthalmic assistants, using standardised methods. A third independent consulting ophthalmologist was employed to evaluate the field work during the study.

Visual acuity was measured with a standard Snellen's E chart at 6 m in shaded daylight. Cataracts (central lens opacities) were identified and graded according to a simple method that has been shown to have excellent interobserver agreement.[6] The principal cause of any visual impairment below 6/12 was determined, with particular care to distinguish between cataract and other disorders as the main causes. Subsequently, in 1986, the people in the study sample were located, examined, and interviewed by the same standardised methods.

The data were entered into a specially designed relational database by means of a microcomputer and were subsequently analysed with software developed at ICEH in London. The exact period of follow-up was computed for each person so that precise person-time denominators could be calculated. The follow-up times for those who died before the final examination were estimated by ascertaining the time of death through interviews with the family. To ensure that the incidences would not be overestimated, persons who could not be re-examined at the follow-up visit were considered to have been followed up and not to have gone blind from cataract. Furthermore, in computing the number of new cases of cataract blindness, persons younger than 35 in the population were considered to have a minimal incidence, which was taken as zero, because none of these young people became blind from cataract. Infants and children becoming blind from congenital cataract were not included in the projected estimates.

Incidence rates with person-time denominators were computed for each 5-year age stratum. The age specific incidence rates were then applied to the age stratified 'at risk' population of the study area and also of the whole country to arrive at the number of new cases of cataract blindness that occur per year. In addition the 1-year cumulative incidence for each age stratum was derived from the incidence rate of the stratum by the density method.[7] The equation used was: $CI = 1 - e^{-Rt}$ where CI is the cumulative incidence in time t (t being taken as 1 year), R is the incidence rate per year), and e is the constant 2·71828, the base of natural logarithms. Unlike the incidence rate, the cumulative incidence is not a rate but a proportion, and may be expressed as an absolute number, or a percentage of the original cohort, who became cases *in a specified time period*. The incidence rate on the other hand measures the average speed of occurrence of new cases, and it may be interpreted as the average number of new cases that have occurred *per unit of time* during the study period.

The age specific cumulative incidence proportions were also used to estimate the number of new cases that occur in one year in the country.

The age stratified population for India was based on the United Nations publication ST/ESA/SER.R 170. The population 'at risk' were determined by excluding from the whole population those who were already blind or had had cataract surgery. The expected numbers of these prevalent cases were provided by our cross-sectional survey at the beginning of the study.

An incident case was defined as a person who was not blind at the beginning of the study but became blind (according to the WHO categories 3, 4, 5: vision less than 3/60 in both eyes) because of cataract by the end of the study.

## Results

There were 1735 persons aged 30 and older in the sample. Of these, a cohort of 1655 persons were at risk of becoming blind during the study. The remainder were either already blind or had had cataract surgery. During the follow-up period 6% of the study cohort died.

The incidence rate of cataract blindness in the at risk cohort was 0·0019 per person-year for the age group 35–39 and 0·0581 per person-year for the age group 65 and older. The corresponding annual cumulative incidences were 0·19% and 5·64%. The estimated number of new cases of cataract blindness which occur in the sampled population of Arang was 470 new cases per year per 100 000 persons at risk. The projected estimate for the whole country was 3 811 185 new cases of cataract blindness per year, with approximate 95% confidence limits of 3 to 4·5 million. The details are shown in Table I. The estimate derived from the cumulative incidence was 3 738 947 new cases in one year. This amounts to 0·46% of the population at risk.

TABLE I *Incidence of blindness from cataract in India. Projections from a population based follow-up study in Central India*

| *Age* | *Population** | *Population at risk* | *Incidence rate/person-year* | *Projected number of new cases of cataract blindness per year* |
|---|---|---|---|---|
| 0–34 | 579 810 000 | 576 197 477 | 0·00† | 0† |
| 35–39 | 50 376 000 | 50 205 811 | 0·00190 | 95 486 |
| 40–44 | 41 665 000 | 41 301 114 | 0·00253 | 104 473 |
| 45–49 | 35 783 000 | 35 203 518 | 0·00595 | 209 610 |
| 50–54 | 31 654 000 | 29 867 081 | 0·01336 | 399 157 |
| 55–59 | 27 369 000 | 25 138 933 | 0·02388 | 600 218 |
| 60–64 | 22 088 000 | 18 182 195 | 0·03734 | 678 842 |
| 65+ | 38 407 000 | 29 660 851 | 0·05810 | 1 723 399 |
| Totals | 827 152 000 | 805 756 980 | | 3 811 185‡ |

*Population of India: based on United Nations publication ST/ESA/SER.R 170. †Very low incidence in the population; taken as zero, since no incident cases occurred in the sample. ‡Approximate 95% confidence limits = 3 to 4·5 million.

TABLE II *Age and sex distribution of the study sample and age specific follow-up times in person-years*

| | *Males* | | *Females* | | *Males+females* | | |
|---|---|---|---|---|---|---|---|
| *Age* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *Person-years follow-up* |
| 30–34 | 124 | 15·92% | 191 | 19·98% | 315 | 18·16% | 1123·92 |
| 35–39 | 110 | 14·12% | 186 | 19·46% | 296 | 17·06% | 1055·58 |
| 40–44 | 120 | 15·40% | 109 | 11·40% | 229 | 13·20% | 797·66 |
| 45–49 | 134 | 17·20% | 113 | 11·82% | 247 | 14·24% | 854·16 |
| 50–54 | 98 | 12·58% | 150 | 15·69% | 248 | 14·29% | 867·33 |
| 55–59 | 68 | 8·73% | 67 | 7·01% | 135 | 7·78% | 455·24 |
| 60–64 | 77 | 9·88% | 87 | 9·10% | 164 | 9·45% | 541·99 |
| 65+ | 48 | 6·16% | 53 | 5·54% | 101 | 5·82% | 329·16 |
| Totals | 779 | 100·00% | 956 | 100·00% | 1735 | 100·00% | 6025·04 |

About 0·6% of the original cohort of 315 persons aged 30–34 developed cataract in at least one eye during the study. However, none of these were blinded by cataract in the sample, reflecting a very low incidence rate of cataract blindness in this stratum of young people. The age and sex distribution of the study sample, together with the follow-up times in person-years, are shown in Table II.

## Discussion

The projected numbers of new cases of blindness from cataract should be considered as minimal estimates because of the following considerations. First, since there were no incident cases of cataract blindness in the youngest age cohort in the sample (younger than 35), the incidence in that population stratum was considered to be very small and was taken as zero. Secondly, persons who could not be examined at the end of the study were included in the denominators and were counted as non-cases. This was mostly justified because by far the commonest reason for being absent at the time of the second survey was new employment. These persons were not likely to be blind. In this follow-up study 80·2% of the original cohort were successfully located again and re-examined (if alive) at the end of the follow-up period. Thirdly, blindness and aphakia prevalence measures were used to exclude those who were already blind (or had had cataract surgery), so that only the populations at risk of becoming blind were used in computations. Finally, new cases of blindness from congenital cataract were not included in the estimates. The projection for the whole country assumes that the age specific incidence rates in the population of the Arang Block in Central India are fairly similar to the average incidence rates for the country.

At present some 1·2 million cataract extractions are performed in India each year. In spite of this huge effort evidence from recent prevalence data indicates that cataract blindness is increasing (survey conducted by the National Blindness Prevention and Control Programme/World Health Organisation). This has led to a recent suggestion that the ophthalmic services in India should aim to do more than 2 million cataract operations each year. Our findings suggest that the cataract blindness problem in India is too massive to be solved by the surgical programme alone, particularly in view of the aging population trend which is expected substantially to increase the number of new cases of blindness from cataract. Moreover, even under very favourable conditions, cataract surgery is not entirely free of risk. Some of the effort in control of cataract blindness should be directed at developing strategies to reduce the incidence of blinding cataract. Our earlier findings on dehydrational crises as a major risk factor for cataract[8 9] offer an opportunity to initiate and test community based interventions to control dehydrational crises and perhaps to control other important risk factors that may be identified through further epidemiological research, thus aiming to reduce substantially the number of new cases of cataract blindness that occur each year.

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# Cyclosporin in the treatment of severe chronic idiopathic uveitis

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## Abstract

**In a randomised double-masked study of 27 patients with a severe chronic idiopathic uveitis we evaluated the efficacy, safety, and tolerability of cyclosporin. All received prednisone in a low dose (0·3 mg/kg/day). In 14 patients this was combined with cyclosporin in a single daily dose of 10 mg/kg/day, while 13 patients received a placebo. The dosages were tapered off in accordance with a protocol, and we compared the number of months of successful therapy before the uveitis relapsed. The efficacy results, as expressed in a Kaplan-Meier curve, were in favour of cyclosporin. Owing to the small sample size, however, this difference did not reach statistical significance. The immunosuppressive effect of cyclosporin was not permanent, and in all but one patient the intraocular inflammation relapsed on reduction of dosage. Rather small cumulative doses of cyclosporin proved to be nephrotoxic, but subjective tolerablity for cyclosporin was good.**

Uveitis is a collective term for a variety of intraocular inflammatory diseases located in the iris, ciliary body, choroid, retina, and/or vitreous body. In approximately 20% of the patients an infection such as *Toxoplasma gondii*, toxocara, candida, *Mycobacterium tuberculosis*, *Treponema pallidum*, or herpes viruses can be established.[1] The other uveitis cases are 'idiopathic', though in most of the patients a clinical entity like Behçet's disease, sarcoidosis, or birdshot retinochoroidopathy can be diagnosed.

For these cases of 'idiopathic' uveitis corticosteroids are the mainstay of therapy. In severe chronic idiopathic uveitis chemotherapeutic agents such as chlorambucil and azathioprine are the only recourse if corticosteroids are ineffective or not tolerated. Most physicians are reluctant to use chemotherapeutic agents, however, because of potential toxicity including neoplasia, bone marrow depression, secondary opportunistic infection, and sterility. The introduction of cyclosporin, a new immunosuppressive agent, offered the hope of a safer and more effective therapy for patients with an intractable, blinding uveitis.

Experience in organ transplantation proved that cyclosporin can effectively prevent the initiation of an immune response to foreign antigens.[2-4] In idiopathic uveitis, however, the situation is completely different. Here the immune response is already in full swing with (auto)antigens recognised, helper cells activated, and effector clones established. Little is known about the therapeutic instead of preventive use of cyclosporin. Preliminary data like the effects on second set rejection of allografts in animal[5-7] and man,[8] the results in the treatment of graft-versus-host disease in man,[9] and the effects in experimental animals of uveitis [10-13] imply its possible usefulness.

In 1983 Nussenblatt and associates[14] published the first study in which cyclosporin was used as a treatment of intraocular inflammatory disease in man. They concluded that 'cyclosporin A appears to be an effective alternative to the present therapies'. Since then similar results have been found in other case reports and pilot studies.[15-21]

Until now no double-masked placebo-controlled studies have been published in which these first impressions have been either rejected or confirmed.

## Patients and methods

### ORGANISATION

Four ophthalmological departments participated in this study. The Rotterdam Eye Hospital (the Department of Ophthalmology of Erasmus University) was responsible for collecting and analysing the data. The Netherlands Ophthalmic Research Institute provided communications.

### STUDY DESIGN

The investigation was designed as a randomised, double-masked, placebo-controlled clinical trial. The factors analysed were the efficacy, safety, and tolerability of cyclosporin.

After obtaining informed consent each patient was allocated in a strictly consecutive order to either the cyclosporin group or the placebo group according to a randomisation list. After inclusion in the study the patients were reexamined at week 1, 2, and 4 and at one-month intervals thereafter for up to one year.

All patients were monitored by the same two investigators throughout the study. One masked investigator, with no information about the assigned treatment, evaluated the efficacy parameters and decided about possible changes in therapy according to the protocol. A second investigator who knew the assigned treatment checked the safety parameters and recorded the subjective side effects.

### ELIGIBILITY CRITERIA

Patients were eligible for admission to the study if they had an active idiopathic posterior uveitis, panuveitis or intermediate uveitis, an insufficient response to systemic corticosteroids, and a best corrected visual acuity of 0·5 or less in their best eye. This last criterion did not apply for patients with Behçet's disease or sympathetic ophthalmia, since they can be well separated from the other uveitis cases and since their poor prognosis under current therapy is well documented.[22 23]

The following exclusion criteria were applied: age under 18, presumed infectious uveitis, end-stage disease with irreversible retinal damage, corneal or lens opacities preventing the evaluation of the efficacy parameters, anticipated intraocular surgery during the study, contra-indications to immunosuppression (that is, uncontrollable infections, malignancy, or a history of malignancy), contraindications to oral corticosteroid therapy, concomitant therapy with cytostatic agents or nephrotoxic medicines, impaired kidney or liver function, hypertension, pregnancy, malabsorption syndrome, drug or alcohol abuse, and non-cooperation.

### TREATMENT PLAN

At entry into the study all patients received a low dose of prednisone (0·3 mg/kg/day to a maximum of 20 mg/day). In one group this was combined with cyclosporin in a single dose of 10 mg/kg/day, while the second group received a placebo instead. After two weeks of therapy and depending on the clinical response (see below) the corticosteroid dosage was reduced by 2·5 mg per fortnight and eventually stopped. After oral corticosteroids had been tapered off to zero, cyclosporin (or placebo) was reduced by 1 ml (=100 mg) per month. In Figure 1 an example is given of the dose reduction protocol for a 70 kg patient, in case of treatment success. The dosages were tapered off in accordance with protocol in order to compare the two treatment groups with regard to the number of months of successful therapy before the uveitis relapsed. The dosage of corticosteroids or cyclosporin (or placebo) could be kept constant only in case of a decrease in visual acuity of 1 rank number (see efficacy parameters), compared with the best visual acuity, owing to uveitis, or in case of an unchanged visual acuity in combination with an increase in inflammatory activity score of more than 4 points.

For safety reasons the dose of cyclosporin drink solution could be reduced by 25% in case of a predose (24 hours after the last dose) cyclosporin concentration in whole blood exceeding 1000 ng/ml, an increase of serum creatinine level above 150% of the baseline value, an increase of the liver function parameters above 200% of the upper normal limits, or hypertension (diastolic blood pressure above 95 mmHg for age ≤50 or above 100 mmHg for age >50). In order to safeguard the double-masked design of the study dose reductions were also made in the placebo group. The dosage of corticosteroids or cyclosporin (or placebo) could not be increased. The only concomitant medication for uveitis allowed was dexmethasone 0·1% and/or atropine 1% eye drops. Subconjunctival or parabulbar injections of corticosteroids were not allowed.

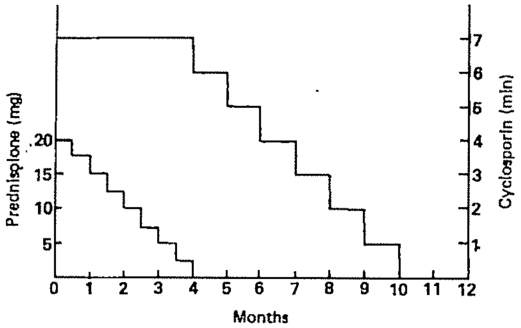

*Figure 1: Example of the dose reduction protocol for a 70 kg patient in case of treatment success.*

A combination therapy was given because a double-masked comparison of cyclosporin versus prednisone was not possible owing to the different administration forms and the outward side effects of corticosteroids. Prednisone was given in a low dose to avoid over-immunosuppression and the resulting increased susceptibility to malignant neoplasms and infections.

### EFFICACY PARAMETERS

The main efficacy parameter was the visual acuity. The best corrected visual acuity was determined at 6 m with charts which contain Landolt C optotypes ranging in unequal steps from a visual angle of 10′ (that is visual acuity 20/200) to one of 0·5′ (visual acuity 20/10). When the visual acuity of a patient was below 20/200 a second ordinal scale was used, namely, finger counting (FC), hand movements (HM), light perception (LP), and no light perception (NLP).

In order to make comparisons between the two measurement scales the visual acuity of each eye was given a rank number. For example, visual acuities of hand movements in one eye and 20/80 in the other were given the rank numbers 2 and 8 respectively.

The second efficacy parameter was the inflammatory activity. This was assessed by using a slightly modified Hogan-Thygeson-Kimura scale.[24] This scale is shown in Table I. The inflammatory activity score was the sum of the scores of the individual scores. Owing to the large variety of signs and symptoms included in the scale, a maximal score of 52 could theoretically be reached. In the clinical setting, however, this maximal score could not be reached because the severity of one parameter made impossible

TABLE I *Inflammatory activity score*

| *Parameter* | *Score* | | | | |
|---|---|---|---|---|---|
| Congestion | 0* | | 2 | | 4† |
| Keratic precipitates | 0 | | 2 | | 4 |
| Anterior chamber flare | 0 | 1 | 2 | 3 | 4 |
| Anterior chamber cells | 0 | 1 | 2 | 3 | 4 |
| Vitreous opacity | 0 | 1 | 2 | 3 | 4 |
| Macular oedema | 0 | | 2 | | 4 |
| Optic disc oedema | 0 | | 2 | | 4 |
| Vasculitis | 0 | | 2 | | 4 |
| Infiltrates | 0 | | 2 | | 4 |
| Snowballs | 0 | | | | 4 |
| Snow banks | 0 | | | | 4 |
| Exudates | 0 | | | | 4 |
| Haemorrhages | 0 | | | | 4 |

*Absent; †Strongly present.

the evaluation of other more posteriorly situated parameters, that is, vitreous opacity versus macular oedema.

### SAFETY PARAMETERS

The following safety parameters were recorded: cyclosporin blood level, serum creatinine, urea nitrogen, serum aspartate transaminase (SGOT), serum alanine transaminase (SGPT), bilirubin, γ-glutamyl transpeptidase (γ-GT), lactic dehydrogenase (LDH), haemoglobin, white blood cell and differential counts, platelets, erythrocyte sedimentation rate, blood pressure, pulse rate, and body weight in standardised conditions. Cyclosporin blood levels were measured by using the radioimmunoassay kit manufactured by Sandoz (Basle, Switzerland). Cyclosporin was taken orally once daily at breakfast. Patients were instructed to postpone taking their medication on the morning of re-examination to allow determination of the predose cyclosporin blood level.

### END POINTS

For the individual patient the study lasted one year. A premature termination was considered as either 'treatment failure' or 'drop out'. A treatment failure was defined as (*a*) a decrease in visual acuity of ≥2 rank numbers compared with the best visual acuity, due to uveitis, or (*b*) an unchanged visual acuity in combination with an increase in inflammatory activity score of ≥4 points, or (*c*) a discontinuation of the medication because of side effects which did not respond to dose reduction. A patient was considered a drop-out in case of withdrawal of consent; non-compliance, intraocular surgery, occurrence of contraindications to immunosuppression, pregnancy, or when lost to follow-up

### STATISTICS

The findings from all the patients who entered the study were analysed. To account for those patients who dropped out during the study the efficacy results were expressed in Kaplan-Meier estimates of the 'survival' curves for the two treatment groups.

The two-sided Wilcoxon's rank sum test was used for quantitative variables and the log rank test for the comparison of the 'survival' curves.

The study protocol was approved of by the ethical committees of the participating university hospitals.

## Results

Twenty-seven patients with a chronic idiopathic posterior uveitis, panuveitis, or intermediate uveitis entered the study. All patients had been unsuccesfully treated with high doses of systemic corticosteroids previously. Two patients had also recieved cytostatic agents on previous occasions. In all cases an active intraocular inflammation of non-infectious origin was present at entry. Fourteen patients were randomly allocated to cyclosporin and 13 to placebo. Table II summarises the background characteristics of the patients.

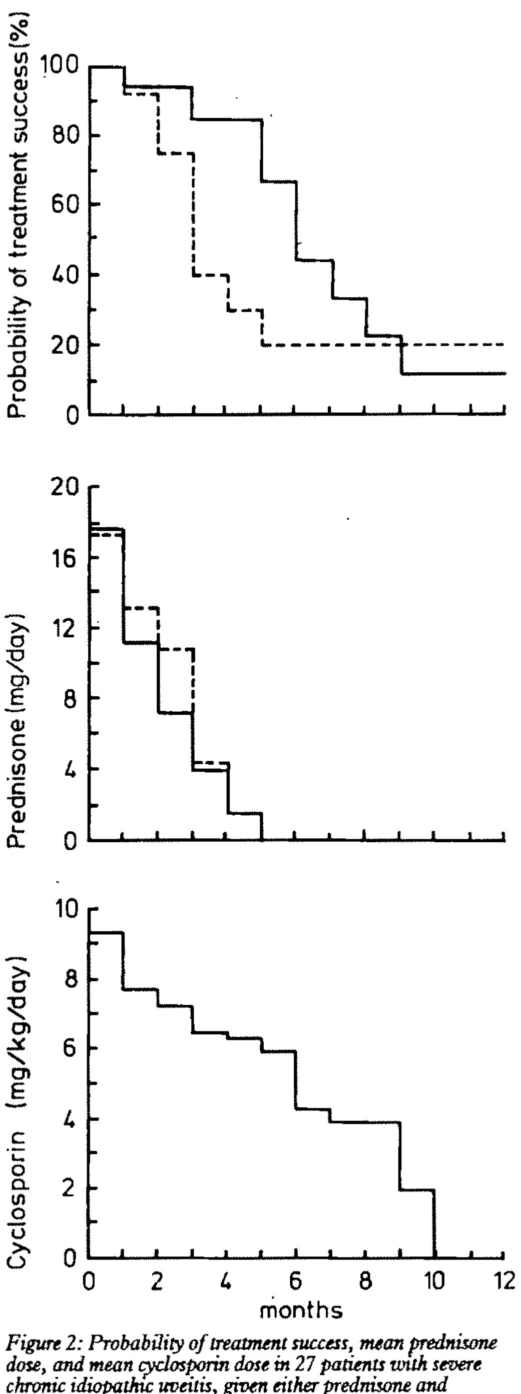

*Figure 2: Probability of treatment success, mean prednisone dose, and mean cyclosporin dose in 27 patients with severe chronic idiopathic uveitis, given either prednisone and cyclosporin (continuous line) or prednisone and placebo (dotted line).*

TABLE II *Comparison of treatment groups*

| *Characteristic* | *Cyclosporin* | *Placebo* |
|---|---|---|
| Number of patients | 14 | 13 |
| Male/female ratio | 6/8 | 7/6 |
| Age (yr) | 44·5 (19·5, 22–74)* | 45·6 (15·9, 26·75) |
| Visual acuity | 20/125 (FC, 20/64)† | 20/125 (FC, 20/80) |
| Inflammatory activity | 12·3 (6·2, 3–24) | 11·9 (4·1, 5–20) |
| Duration of disease (yr) | 5·6 (4·2, 1–16) | 6·5 (6·2, 1–26) |
| Body weight (kg) | 67·5 (9·5, 53–86) | 67·8 (9·6, 52–86) |
| Diagnostic subgroups: | | |
| Behçet's disease | 3 | 1 |
| Intermediate uveitis | 4 | 5 |
| Birdshot retinochoroidopathy | — | 1 |
| Sarcoidosis | 2 | 1 |
| Vasculitis | — | 1 |
| Panuveitis | 3 | 2 |
| Chorioretinitis | 2 | 2 |

*Mean with SD and range in parenthesis. None of the differences between the groups was statistically significant at the 5% level; †FC=finger counting.

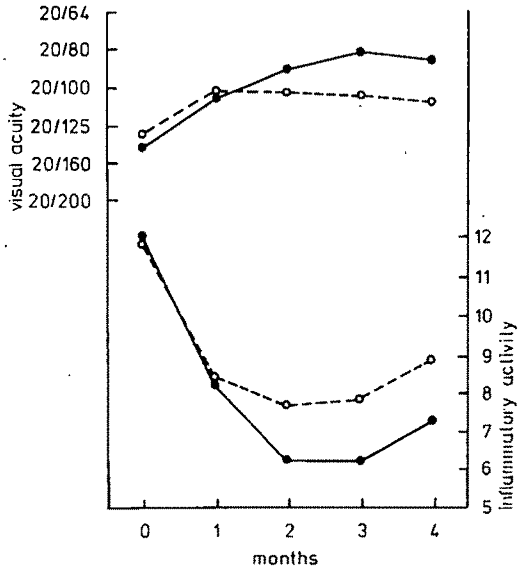

*Figure 3: Course of the mean visual acuity and mean inflammatory activity in 27 patients with severe idiopathic uveitis, given either prednisone and cyclosporin (continuous line) or prednisone and placebo (dotted line). p>0·05. Wilcoxon's rank sum test, two sided.*

None of the differences between the groups was statistically significant at the 5% level. Only one patient of the cyclosporin group had a visual acuity of more than 0·5 in his best eye at entry. This patient had Behçet's disease.

## EFFICACY

The efficacy results are presented in Figure 2. The cyclosprin group fared better than the placebo group in number of months of successful therapy. However, the positive effect of cyclosporin was not lasting after dose reduction, and the difference between the two 'survival' curves did not reach statistical significance (p=0·155, log rank test).

The cyclosporin concentration in blood at the moment of withdrawal from the study because of treatment failure ranged from 0 to 781 μg/l, with a mean at 286 μg/l. All nine patients of placebo group still used prednisone (mean 12·2, range 5–20 mg/day) at that moment, whereas for only three patients of the cyclosporin group this was still the case (5, 10, and 20 mg/day, respectively).

As shown in Figure 3, the course of the mean visual acuity and inflammatory activity appeared to be the same for both treatment groups. A synergistic immunosuppressive effect of the combination of prednisone and cyclosporin could not be demonstrated.

In all except two patients treatment failure was due to a decrease in visual acuity of 2 lines or more in comparison with the best visual acuity. The other two patients (one in each treatment group) were withdrawn because of a decrease in visual acuity of 1 rank number in combination with an increase in inflammatory activity score of more than 4 points. Medication never had to be discontinued because of side effects, though in some cases a dose reduction was necessary because the trough cyclosporin blood levels exceeded 1000 mg/l. Only one patient in each group was considered a treatment success during 12 consecutive months. At termination of the study one patient of the cyclosporin group had not yet completed the follow-up period of 12 months.

During the study there were three drop-outs in each treatment group. In the cyclosporin group one patient moved abroad and was lost for follow-up, one did not comply with the protocol, and one developed cataract which made evaluation of the efficacy parameters impossible. In the placebo group one patient had to undergo glaucoma surgery, one developed cataract, and one had unexplained positive cyclosporin blood levels, probably owing to an accidental change in assigned medication. The possibility of false positive cyclosporin blood levels as put forward by Johnston *et al*[25] was rejected because the patient had positive cyclosporin levels on two consecutive occasions and a simultaneous rise in serum creatinine level. Although the particular placebo sample could not be analysed, other samples of the same batch were negative for cyclosporin. The patient was classified as a 'drop-out' at month 6.

## SAFETY

Renal function was assessed by serum creatinine concentrations. Under treatment three patients of the cyclosporin group had an increase in serum creatinine concentration exceeding 50% of the baseline value; one patient for three consecutive months and the others for only one month. Interestingly also one patient of the placebo group had such an increase for one month. This patient was diagnosed as having an intermediate uveitis. No patient received other drugs known to be nephrotoxic. An estimation of the creatinine clearance was made by using the formula of Cockcroft and Gault.[26] Only one patient of the placebo group had a reduction in creatinine clearance exceeding 25% of the baseline value for one month, while four patients in the cyclosporin group had such a reduction (Table III). A trace of proteinuria was occasionally found in three patients of the placebo group and four patients of the cyclosporin group. Only one of these patients also had a reduction in renal function creatinine clearance) during the trial.

All liver function values were normal at the start and only showed minor fluctuations within the normal range during treatment.

The haematological parameters showed very slight fluctuations above or below the normal range during the study. No change in erythrocyte sedimentation rate was noticed, either in the cyclosporin group or in the placebo group.

All patients had a normal diastolic blood pressure at entry (that is, ≤95 mmHg). This remained so for all patients of the placebo group,

TABLE III *Incidence of abnormal safety parameters during therapy of idiopathic uveitis with cyclosporin*

| | *Number of patients* | |
|---|---|---|
| *Safety parameter* | *Cyclosporin* | *Placebo* |
| Creatinin clearance reduction >25% | 4 | 1 |
| Proteinuria | 4 | 1 |
| Bodyweight increase >5 kg | 5 | 3 |
| Diastolic blood pressure increase >15 mmHg | 4 | 0 |

TABLE IV *Side effects as reported by the patients*

| | *Number of patients* | |
|---|---|---|
| *Side effect* | *Cyclosporin (n=14)* | *Placebo (n=13)* |
| Tremor | 4 | 2 |
| Painful paraesthesiae | 4 | – |
| Hot flushes | 4 | – |
| Headache | 1 | 1 |
| Tiredness | 2 | 3 |
| Epigastric burning | 4 | 2 |
| Nausea | 5 | 1 |
| Loss of appetite | – | 1 |
| Constipation | 1 | 2 |
| Belching | – | 1 |
| Hair growth | 4 | 1 |
| Hair loss | – | 1 |
| Pustules | 2 | 1 |
| Gum hyperplasia | 3 | – |
| Numb feeling in the lips | 1 | – |
| Dry mouth | 1 | – |
| Increased urinary frequency | 1 | – |
| Cystitis | – | 1 |
| Sinusitis | 1 | – |
| Influenza-like disease | 1 | – |
| Epistaxis | 1 | – |

whereas in four cyclosporin patients the diastolic blood pressure increased 15–20 mmHg. This rise in blood pressure was controlled by a reduction of salt intake in three patients and chlorothiazide diuretic therapy in one patient. All these patients also had impaired kidney function.

Five patients of the cyclosporin group and three of the placebo group had a rise in body weight of 5 kg or more. Three of these patients, all belonging to the cyclosporin group, also had an impaired creatinine clearance.

### TOLERABILITY

Only one patient of the cyclosporin group and five patients of the placebo group did not complain of side effects. A large variety of side effects were reported. They are listed in Table IV. The painful paraesthesias were found to be the most annoying side effect. One patient's denture did not fit any more because of gingival hyperplasia. None of the patients requested a dose reduction.

## Discussion

The results of our study suggest that cyclosporin has a suppressive effect on the course of an ongoing immune response in the form of a severe idiopathic posterior uveitis, panuveitis, or intermediate uveitis, but that this effect is not lasting after dose reduction in which the predose blood concentrations of cyclosporin fall below 200–300 μg/l. The data, however, did not reach statistical significance at the 5% level. Although it should be noted that our method of using cyclosporin was chosen for the purpose of the investigation, our findings are in accordance with previously published pilot studies. Müftüoglu and associates[18] treated 11 patients with Behçet's disease with three-month courses of cyclosporin. They observed a rebound phenomenon in all but one patient on the withdrawal of the medication. Similar findings were reported by Graham and associates,[19] who treated nine patients with severe refractory posterior uveitis. In five patients the uveitis relapsed after dose reduction or withdrawal of cyclosporin. At that moment four patients had been treated for three to six months and one for only three days. All seven patients with Behçet's disease treated by Nussenblatt and associates[20] required continuation of cyclosporin therapy after six to 21 months.

In evaluating the beneficial effect of cyclosporin in our study we have to take into consideration the possibility that cyclosporin may reduce the elimination of corticosteroids in the liver, resulting in higher blood concentrations and a potentiation of the effects of prednisone.[27,28] The pharmacokinetic interactions between corticosteroids and cyclosporin, however, are far from completely characterised, and a recent study by Frey and associates[29] contradicted these earlier reports.

It is difficult to believe that this possible prednisone potentiating effect is the only mechanism of action of cyclosporin in uveitis. First, the corticosteroid induced lymphocytopenia and eosinopenia did not significantly differ between both treatment groups. And, second, in six of the nine patients considered a treatment failure one to seven months elapsed between discontinuation of prednisone and the relapse of uveitis. It seems unlikely that a reported 2–5-fold increase of the plasma half-life of corticosteroids (that is, 3–7 h) is responsible for this effect in patients receiving only low doses of prednisone.

Cyclosporin is a nephrotoxic drug.[30] Four patients of the cyclosporin group had a reduction in creatinin clearance exceeding 25% of the baseline value during the study. None of them had pre-existent hypertension, diabetes mellitus, sarcoidosis, or Behçet's disease, and all had a normal pretreatment creatinin level. In one of them serum creatinin levels still remained approximately 40% above baseline values four months after cyclosporin was discontinued. On the basis of the findings of Palestine and associates[31] and Svenson and associates[32] one can expect morphological damage like an arteriolopathy and a striped form of interstitial fibrosis with tubular atrophy in the kidneys of this patient. It is noteworthy that such a reduction in renal function could occur at rather small cumulative doses – namely, 1311 mg/kg over a period of five months and with a cyclosporin predose blood level never exceeding 400 μg/l. This is the more alarming since cyclosporin does not seem to offer a definite cure for uveitis and in all probability therefore has to be administered for longer periods. Moreover some types of uveitis such as sarcoidosis and Behçet's disease may be accompanied by a reduced kidney function. On the other hand the side effects of corticosteroids may also be serious. Before entering the study one of our patients, for example, had a vertebral fracture with spinal cord compression due to osteoporosis. Transition to cyclosporin therapy can offer the opportunity to recover from the side effects of prolonged systemic corticosteroid therapy without resort to antineoplastic chemotherapy or a reactivation of the intraocular inflammation.

In contrast to Palestine and associates[33] we failed to detect any relationship between cyclosporin treatment and erythrocyte sedimentation rate or haemoglobin concentration, neither in the individual patient nor in the two groups as a whole. None of the patients became anaemic during this study.

Our patients personally tolerated cyclosporin well, and the diverse reported subjective side effects vanished before the intractable uveitis they all had. None of them therefore demanded a dose reduction.

In conclusion, the results of this double-masked placebo-controlled study indicate that cyclosporin has a place between corticosteroids and cytostatic agents in the treatment of severe chronic idiopathic uveitis.

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# Ocular penetration of cyclosporin A. III: The human eye

David BenEzra, Genia Maftzir, Christian de Courten, Pentti Timonen

## Abstract

**The distribution of cyclosporin A (CsA) in the blood, saliva, tears, aqueous humour, vitreous, and cerebrospinal fluid has been studied after oral treatment with 5 mg/kg/day of CsA or application of 2% CsA eye drops in olive oil solution. After oral treatment all patients had high CsA levels in blood. Measurable levels of CsA were also found in the saliva and tears. Patients without any intraocular inflammation or patients with mild uveitis did not have any detectable CsA in the aqueous humour. However, patients with severe uveitis had significant levels of CsA in the aqueous humour and in the vitreous. No CsA was found in the cerebrospinal fluid of two patients with central nervous system manifestations of Behçet's disease. After local treatment with 2% CsA eye drops no detectable levels of CsA were found in the blood, the saliva, the aqueous humour, or the vitreous even in patients with severe uveitis.**

Despite intensive treatment with corticosteroids and/or cytotoxic drugs the visual outcome in chronic endogenous uveitis and more so in uveitis accompanying Behçet's disease is extremely poor.[1] Because of the relentless loss of vision leading to blindness in most of these cases many forms of treatment have been tried. None, however, was satisfactory.[1]

With the emergence of the new immunomodulating drug cyclosporin A (Sandimmun) as an effective treatment in kidney transplantation[2] its effects on experimental autoimmune uveitis (EAU) were studied.[3] Owing to the benefits of CsA in the experimental animal clinical studies have been initiated. In most of them the drug was found to be effective in abating the acute intraocular inflammation and preserving vision, even in uveitides refractive to conventional therapy.[4-7] However, the nephrotoxic risk of its prolonged use has inhibited its systemic use for the routine treatment of uveitis.[8,9] To reduce the risk of toxicity of systemic treatment the possibility of using local applications has been investigated.

We report here our observations on the penetration of cyclosporin A into the human eye after local ocular application or systemic ingestion of the drug.

## Materials and methods

### PATIENTS

Twelve patients (nine males and three females) with ocular Behçet's disease (groups 1 and 2), three patients with neuro-Behçet's disease (two males and one female, group 3), and six male patients undergoing routine cataract extraction without any ocular inflammation (group 4) were included in this study. In the ocular Behçet's disease groups six patients suffered from severe panuveitis at least in one eye (group 1) and six patients had signs of mild anterior uveitis with posterior involvement mainly in the peripheral fundus in one or two eyes (group 2).

In groups 1, 2, and 4 three of the six patients were either under systemic treatment with CsA or received 5 mg CsA per kg at 36 hours and 12 hours before sampling was carried out. Three patients from each of these groups were given six eye drops of 2% CsA in olive oil during the 36 hours preceding the sampling. The last eye drop was given one hour before the tests were carried out.

### COLLECTION OF SAMPLES

All fluid samples from each patient were collected within an hour. 2 ml of blood was withdrawn from the cubital vein into a heparinised syringe.

Excreted free saliva or saliva obtained after direct cannulation of the parotid gland was tested as previously described.[10] Tears were aspirated into a 100 μl pipette after introducing a grain of NaCl into the lower cul-de-sac.

Aqueous humour sampling was carried out after thorough washing of the ocular surface with isotonic saline solution. The procedure was explained to the patient and performed after obtaining verbal consent. Under local anaesthesia with oxybuprocaine (Novesine) eye drops 0·2%, 100 μl of aqueous humour was withdrawn by tapping the anterior chamber at the upper limbus with a tuberculin syringe and a 30 G needle.

Only four vitreous samples were studied. They were obtained from patients needing therapeutic vitrectomy. Two of the samples were obtained from patients in group 1 under systemic treatment with cyclosporin A. Two samples were

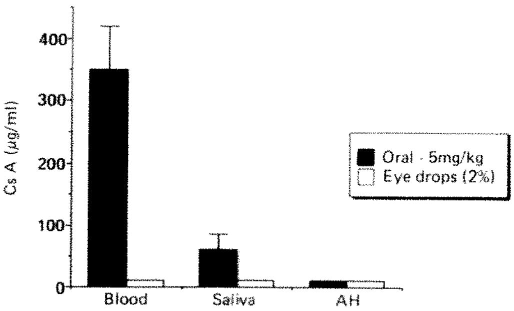

*Figure 1: Levels of CsA observed among patients undergoing routine cataract extraction. The drug was given either orally (5 mg/kg) or locally in 2% eye drops in oil solution. AH = aqueous humour.*

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obtained from patients with severe unilateral panuveitis treated with systemic steroids. These two patients were given CsA eye drops as described earlier before vitrectomy was carried out.

Cerebrospinal fluid (CSF) was obtained from only two patients by direct puncture of the spinal space under local anaesthesia.

25 μl of the intraocular and cerebrospinal fluids were used for bacterial and viral cultures. 25 μl were absorbed on a filter paper for cytology and the remaining 50 μl (or more) were used for the assessment of the CsA levels.

All samples were kept at −80°C until tested.

### EVALUATION OF CsA LEVELS

Samples were thawed at room temperature and testing carried out with the polyclonal antibodies to CsA and its metabolites. The standard curves for detection of CsA levels were prepared according to the guidelines provided with the RIA kits of Sandoz, Basle. However, for dilution of the CsA standards (yielding known concentrations of the drugs) various fluids obtained from normal (control) animals were used and separate standard curves were prepared. The CsA level in each sample of blood, saliva, spinal fluid, tears, aqueous humour, and vitreous was estimated by reference to the appropriate standard curve for each of these fluids. New standard curves were prepared for each batch of tests. To increase further the accuracy of these standard curves fluid samples with known CsA levels obtained during the previous tests were also included in a masked manner. If more than a 15% difference in the CsA level of the repeated samples was obtained, the standard curves were repeated.

In five aqueous humour samples the levels of CsA were also estimated by high-performance liquid chromatography (HPLC).

## Results

When cyclosporin A was ingested orally (5 mg/kg/day), patients without any intraocular inflammation had a mean blood level of 350 μg/l. Detectable levels of the drug were also observed in the saliva of these patients. However, no CsA was found in the aqueous humour in these cases (Fig 1). The aqueous humours did not show any detectable levels of CsA when the tests were repeated by HPLC. After local application of the 2% CsA eye drops in this group of patients, all fluid samples were devoid of any measurable CsA (Fig 1).

Patients with mild posterior uveitis accompanying the manifestations of ocular Behçet's disease had no detectable levels of CsA in the aqueous humour after oral or local treatment (Fig 2). Low levels of CsA were detected in the tears and saliva of those patients treated systemically with 5 mg/kg/day of cyclosporin A (Fig 2).

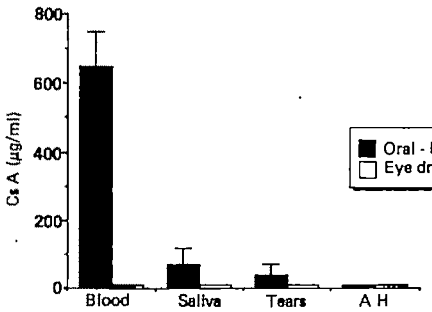

*Figure 2: Levels of CsA observed among patients with mild uveitic manifestations of ocular Behçet's disease. AH= aqueous humour.*

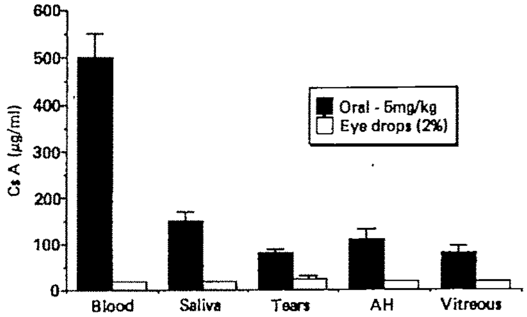

*Figure 3: Levels of CsA observed among patients with severe uveitic manifestations.*

In the group of patients with ocular Behçet's disease and severe panuveitis, 'treatment' with local eye drops did not induce any intraocular penetration of CsA. However, after systemic treatment high levels of CsA were found in the aqueous humour and in the vitreous (Fig 3). Systemic treatment resulted also in measurable levels of the drug in the saliva and tears of these patients. Measurable levels of CsA in tears were observed only in one of the patients in this group treated with eye drops (Fig 3).

The distribution of CsA in patients with Behçet's disease and central nervous system involvement was similar to that observed in the other groups after systemic treatment with the drug. In the cerebrospinal fluid, however, no measurable levels of CsA were observed (Fig 4).

## Discussion

The data obtained in this study demonstrate that in the human eye topical instillation of 2% CsA in olive oil does not result in any measurable levels of the drug in the aqueous humour or the vitreous even in eyes with severe panuveitis. These results correlate well with our previous observations in the rabbit (BenEzra and Maftzir, to be published) and rat eyes (BenEzra and Maftzir, to be published) using radioactive and non-ratioactive CsA in inflamed or non-inflamed eyes.

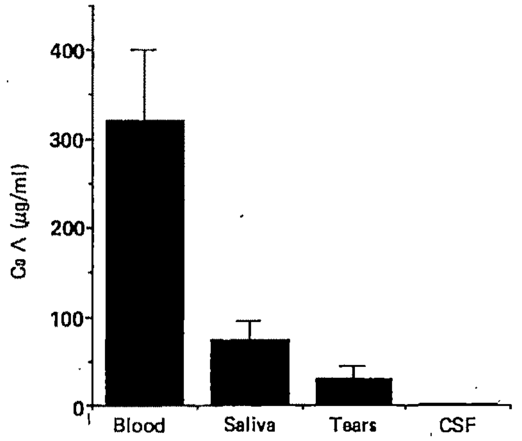

*Figure 4: Levels of CsA observed among patients with CNS manifestations of neuro-Behçet's disease.*

The findings of CsA in the aqueous humour of rabbit eyes following corneal grafting as reported by others[11] may be explained by the possible 'easier' penetration of the drug via the wound between the host and graft. However, the relatively high levels of CsA in the contralateral eye of these rabbits as observed by these workers are surprising. Although a 'recirculation effect' has been suggested as the explanation of similar findings,[11 12] in our opinion the strong and tight blood-retinal barrier in the intact eye prevents any possible intraocular penetration via the systemic recirculation. Therefore studies demonstrating intraocular penetration of CsA in untreated healthy contralateral eyes after local application of oil solution (or systemic administration) of CsA should be carefully re-evaluated. Species specific differences regarding the metabolism of CsA have been observed.[13] However, from our studies it appears that the ocular distribution of the drug in the rabbit, the rat, and the human eye is similar.

After oral ingestion of the drug high blood levels have been found in all patients. Significant detectable levels of CsA were also observed in saliva and tears. These results may reflect the high differential uptake of CsA in these glands. Indeed, a high specific uptake of CsA in the salivary glands of experimental animals has been demonstrated.[14] Our study further shows that specific concentration of CsA is probably also taking place in the human lacrimal gland. These findings may be helpful when considering the possible use of CsA in non-infectious inflammatory diseases affecting the salivary and/or lacrimal glands.

Regarding the intraocular penetration of CsA, however, there is a definite and clear differentiation between the findings observed in the non-inflamed or mildly inflamed eyes on the one hand, and the eyes with severe uveitis on the other. Obviously, in the latter, the breakdown of the blood-retinal barrier and the leaky nature of the intraocular blood vessels allow penetration of the lipophilic molecule of CsA into the aqueous humour and vitreous. These results are in line with the observations of measurable levels of CsA in the aqueous humour of a few patients with uveitis[15] and Behçet's disease.[16]

In earlier studies we have observed detectable levels of CsA in the aqueous humour after local application of the drug in rabbit eyes with severe intraocular inflammation (BenEzra and Maftzir, to be published). High levels of CsA in the aqueous humour have also been observed in the rat eye when extensive damage of the cornea was induced by topical application of absolute alcohol eye drops (BenEzra and Maftzir, to be published). In the human eye, however, as shown in this study, no detectable levels of CsA were found either in the aqueous humour or in the vitreous after local application of 2% CsA in olive oil even in eyes with severe panuveitis. These differences between the inflamed rabbit eye and the human eye with uveitis may be due to the fact that the corneas of the inflamed rabbit eyes were oedematous, while in the patients' eyes with uveitis the corneas were not affected.

Our findings clearly demonstrate that detectable levels of cyclosporin A in the human eye are observed only in eyes with severe uveitis after systemic ingestion of the drug. Thus breakdown of the blood-retinal barrier is necessary to allow intraocular penetration of CsA. After topical application of 2% CsA oil solution the drug is not observed within the human eye, even in eyes with severe panuveitis.

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Duzman, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989: *96* (1): 8-11.
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*British Journal of Ophthalmology*, 1990, 74, 353–357

# High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behçet's disease

Howard H Tessler, Tom Jennings

**Abstract**

**We treated five patients with intractable sympathetic ophthalmia and six patients with severe Behçet's disease by high-dose, short-term chlorambucil therapy. We used a total dose ranging from 306 mg to 4·2 g and a duration of therapy no longer than 36 weeks and in most cases less than 24 weeks. After termination of therapy all 11 patients had a sustained remission of their eye disease. Unless subretinal neovascularisation was present, all had a final visual acuity of 20/50 or better. Malignancy has not developed in any of our cases, with a follow-up ranging from 6 months to 12 years (mean, 4·5 years). Although 30- and 40-year follow-ups and larger numbers of patients may be necessary fully to realise the risks of chlorambucil, we believe that our high-dose, short-term regimen (Behçet's disease: average duration, 23 weeks; average total dose 2·2 g; sympathetic ophthalmia: average duration, 11 weeks; total average dose, 0·9 g) may be safer than previously reported chlorambucil regimens of one to two years or longer. In addition we fulfilled our aim of discontinuing all concomitant systemic corticosteroids within a relatively short time (usually six to eight weeks).**

Since the early 1970s[1-4] chlorambucil has been reported to be effective in the treatment of both Behçet's disease and sympathetic ophthalmia (SO). Dosage and length of therapy have varied, and many reports have questioned its safety as an immunosuppressive agent.[5-11]

We attempted to establish a chlorambucil regimen that would be effective and have minimal risks. We herein describe five patients with intractable sympathetic ophthalmia and six patients with severe Behçet's disease who were successfully treated with one-time, short-term, high-dose chlorambucil therapy. We emphasise the importance of this dosage schedule and contrast the results of high-dose, short-term (approximately 6-month) treatment with those of other studies using lower-dose, long-term therapy.[1-4] After the termination of therapy all our patients had a sustained remission of their eye disease. Follow-up ranged from six months to 12 years, with a mean of 4·5 years.

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## Patients and methods

### PATIENTS

The diagnosis of Behçet's disease and SO were made by standard clinical criteria.[12 13] In patients with SO, if there was no potentially useful vision in the exciting eye, such as visual acuity of hand motions or worse, coupled with irreparable retinal detachments or severe anterior chamber derangement, enucleation was recommended. Patients were considered for chlorambucil therapy if they were only partially responsive to high-dose oral corticosteroids or if they had suffered serious side effects of corticosteroids such as diabetes mellitus, uncontrolled glaucoma, or psychological problems. Patients and, when available, their families were told the side effects of chlorambucil along with its potential benefits. Stressed potential side effects included late malignancy and sterility. Patients were not allowed to make an instantaneous decision, and most took one or more weeks to decide about therapy. An informed consent form was signed by all patients or their parents.

Patients without active inflammation and patients with macular scars and/or optic nerve atrophy were not given chlorambucil, because little visual improvement could be expected from immunosuppressive therapy.

### METHODS

Treatment was similar to the regimen described by Godfrey *et al.*[2] Dosing was begun at 2 mg (1 tablet) daily. This low dose provides a margin of safety for an idiosyncratic acute bone marrow depression. In the absence of a white blood cell (WBC) count below $2{\cdot}4\times10^9/l$ or a platelet count below $100\times10^9/l$ the dosage of chlorambucil was increased by 2 mg/day each week. This weekly increase was maintained unless the WBC or platelet parameters were reached or unless there was clinical remission of minimal, low-grade inflammation (trace to 1+ flare or rare, occasional cells) with no active fundus lesions present. If the blood count parameters were reached, the chlorambucil therapy was abruptly terminated.

All patients were receiving oral prednisone at the time of institution of chlorambucil therapy. As they showed a stable or improving clinical response with the increasing chlorambucil dosage, the prednisone dosage was tapered. The goal was to treat the patients with chlorambucil alone without concomitant prednisone therapy. This goal was accomplished slowly, over six to eight weeks.

In all but two cases, when prednisone therapy was entirely discontinued, the chlorambucil dose was increased to compensate for the loss of the anti-inflammatory effects of prednisone. Once low-grade inflammation was achieved, an attempt was made to continue chlorambucil therapy at the same dosage without concomitant prednisone for three months. However, in all but one case the blood cell count dropped to a level described above as too low to achieve a three-month goal. In two cases, when chlorambucil was being used alone, the WBC or platelet counts appeared to be approaching the cut-off levels stated above, the dosage was decreased by 2 to 4 mg daily. In the other cases the dosage was maintained if the disease was stable or steadily increased if the disease was active. After three months of therapy at levels of minimal ocular inflammation or if the WBC level fell below 2·4×$10^9$/l or the platelet count fell below 100×$10^9$/l, chlorambucil therapy was abruptly discontinued. Blood cell counts were followed weekly.

No attempt was made to measure dose by body weight or mass. Patients were given only enough chlorambucil for one week of therapy to guard against their non-compliance.

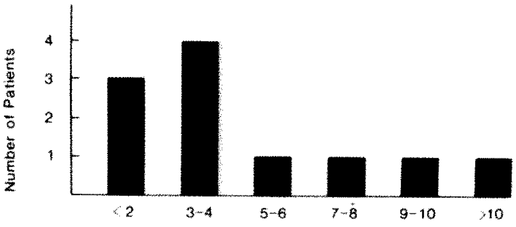

*Figure 1: Distribution of follow-up in patients with Behçet's disease and sympathetic ophthalmia.*

## Results

Twenty-three and 22 patients were diagnosed as having SO and Behçet's disease respectively in the period from 1973 to 1988. Six of 23 patients diagnosed as having SO were treated with chlorambucil. One of the six patients was not included in the series because the chlorambucil was not administered by us or by our dose techniques. The 17 patients not treated with chlorambucil had disease amenable to control with topical, periocular, or systemic corticosteroids. Thus we include five patients with SO in the report.

Six of 22 patients diagnosed as having Behçet's disease were treated with chlorambucil. One patient declined chlorambucil after the side effects were explained. Three patients were thought to have irreparable damage to the retina and were not offered therapy. Twelve patients appeared to have mild ocular disease easily controlled with topical and low- dose short-term prednisone therapy.

Figure 1 shows the distribution of follow-up for patients with SO and Behçet's disease.

When WBC or platelet counts fell to the cutoff levels of 2·4×$10^9$/l or 110×$10^9$/l respectively, these counts usually recovered to normal levels in about six weeks. Once the patients went through this six-week depression, they invariably had a sustained remission with no active inflammation. If the WBC or platelet counts recovered to normal levels sooner (one to three weeks), a second short course of chlorambucil would be required to lower the counts again to achieve that six-week depression period. One patient's counts returned to normal within two weeks when a 2·8×$10^9$/l WBC count was used as the cut-off to discontinue chlorambucil treatment. When we lowered the WBC cut-off to 2·4×$10^9$/l, her WBC counts decreased to low levels (0·9×$10^9$/l to 1·6×$10^9$/l) and slowly recovered over six weeks. Only then did her disease go into sustained remission.

As seen in Table I, no patient had over 36 weeks of treatment. All patients but two, patients 3 and 6, had less than six months of therapy with chlorambucil. The total dose ranged from 306 mg to 4·2 g.

There were notable differences in total dose and duration of therapy when comparing the patients with Behçet's disease and those with SO. The former group received a mean dose of 2·18 (SD 1·10 g, range 1·29 to 4·20 g). The SO group received a mean dose of 0·85 (SD 0·48 g, range 0·31 to 1·53 g; $p=0{\cdot}03$ by Student's *t* test). The duration of chlorambucil therapy was 22·8 weeks (SD 9·0, range 14 to 36 weeks) for the Behçet's group and 11·2 weeks (SD 3·2, range 7 to 15 weeks) for the SO group ($p=0{\cdot}02$, Student's *t* test). The patients' highest daily dosage ranged from 10 to 28 mg. After patient 11 took 92 mg in a single dose during a suicide attempt she recovered and went into sustained complete remission.

Visual acuities before and after chlorambucil therapy are shown in Figure 2. Final visual acuities in the patients with Behçet's disease were all 20/50 or better. Four of the 12 eyes with Behçet's disease had a final visual acuity of 20/20, and seven of the 12 eyes had a post-treatment

TABLE I *Clinical characteristics of patients receiving chlorambucil*

| *Patient no./ age (yr)/sex/ race* | *Initial VA* | | *VA just before chlorambucil therapy* | | *Final VA* | | *Follow-up (yr)* | *Highest dosage (mg/day)* | *Total dose (mg)* | *Duration of therapy (weeks)* |
|---|---|---|---|---|---|---|---|---|---|---|
| | *OS* | *OD* | *OS* | *OD* | *OS* | *OD* | | | | |
| Behçet's disease* | | | | | | | | | | |
| 1/15/M/Ind | 20/80 | 20/80 | 20/50 | 20/60 | 20/40 | 20/25 | 1 | 20 | 1288 | 14 |
| 2/17/F/W | HM | 20/30 | 3/200 | 20/200 | 20/50 | 20/20 | 12 | 22 | 1540 | 25 |
| 3/28/F/W | 20/20 | 20/60 | 20/30 | 20/200 | 20/20 | 20/30 | 1 | 24 | 2688 | 30 |
| 4/26/F/W | 20/25 | HM | 20/25 | 20/60 | 20/20 | 20/40 | 5 | 24 | 1582 | 15 |
| 5/38/F/W | 20/30 | 20/20 | 3/160 | 1/200 | 20/25 | 20/30 | 3 | 22 | 1750 | 17 |
| 6/26/M/B | 20/70 | 20/400 | 20/300 | 20/200 | 20/25 | 20/20 | 7 | 28 | 4200 | 36 |
| Sympathetic ophthalmia | | | | | | | | | | |
| 7/6/F/W | LP | 20/25 | Enuc | 20/40 | Enuc | 20/25 | 9 | 10 | 490 | 9 |
| 8/25/F/H | Enuc | 20/40 | Enuc | 20/40 | Enuc | 20/20 | 2 | 14 | 868 | 12 |
| 9/54/M/W | CF | 20/400 | CF | 20/400 | 4/200+ | 20/200+ | 3 | 18 | 1064 | 15 |
| 10/42/M/B | 20/25 | LP | 20/50 | Enuc | 20/20 | Enuc | 1–2 | 22 | 1526 | 14 |
| 11/16/F/Ind | NLP | 8/400 | NLP | 8/400 | NLP† | 20/200+ | 3 | 92‡ | 306 | 7 |

VA indicates visual acuity; Ind, Eastern Indian; W, white; B, black; H, Hispanic; HM, hand motions; LP, light perception; Enuc, enucleated; CF, counting fingers; and NLP, no light perception.

*All patients had complete Behçet's disease except patient 1; †Subretinal neovascularisation was present; ‡Suicide attempt.

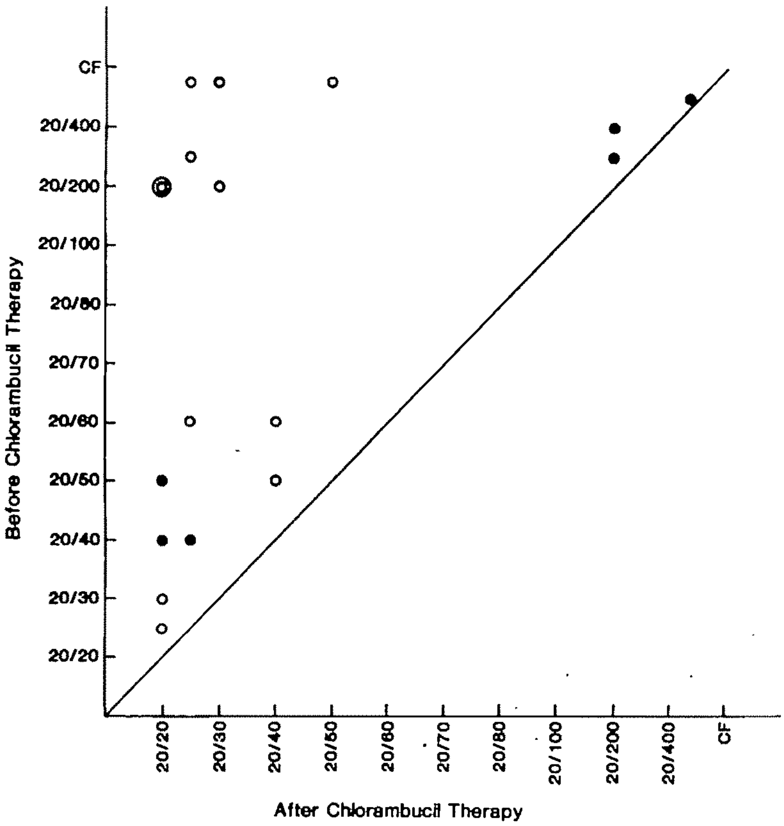

*Figure 2: Visual acuity before and after and chlorambucil therapy in patients with Behçet's disease and sympathetic ophthalmia. Clear circle=Behçet's disease, solid circle=sympathetic ophthalmia. Double circle=two patients.*

acuity of 20/25 or better. Final visual acuities in the patients with SO ranged from 20/20 to 4/200. Patients in this group with less than 20/25 final visual acuity had decreased vision due to subretinal neovascularisation in the macula (Table I).

## Discussion

Chlorambucil is an alkylating agent and has been used successfully as a cytotoxic agent for many non-malignant disorders, including rheumatoid arthritis, glomerulonephritis, and systemic lupus erythematosus.[5,14–16] Chlorambucil is slower to show toxic effects than other alkylating agents, such as cyclophosphamide and nitrogen mustard, and blood counts can be obtained only weekly. Chlorambucil can be administered orally because it is well absorbed from the gastrointestinal tract.[17] Nausea, vomiting, anorexia, and alopecia seldom occur with this drug.[2,18] Thus it is easy to use on an outpatient basis.

Our patients generally had good responses in visual acuity following chlorambucil treatment. All five patients with SO had visual acuities greater than or equal to 20/25 unless there was macular subretinal neovascularisation. All of our Behçet's disease patients had a visual acuity of 20/50 or better. Four of 12 eyes had 20/20 visual acuity, and seven of the 12 had 20/25 or better. Other authors also reported good results in treating intractable SO and Behçet's disease with chlorambucil.[1–4,19–21] In contrast to our dosing method these authors generally administered chlorambucil to the patients for longer periods (one year or longer) and did not try to provoke bone marrow toxicity. In fact some authors[3] specifically stated that a therapeutic goal was to maintain the WBC above $3\cdot5\times10^9$/l. Not infrequently remission was induced after termination of chlorambucil therapy.[1,3,4,21]

Tabbara[10] described 10 patients with Behçet's disease who were treated with chlorambucil; visual acuities of less than 20/200 resulted in 15 of 20 eyes. He did not state how chlorambucil was administered. Differences in patient populations, stages of severity of disease, or treatment regimen may explain the different results. In our series the potential for return of useful vision was a criterion for therapy. We did not give chlorambucil to those patients who appeared to have severely damaged optic nerves or maculas. In Tabbara's report the selection criteria were not stated.[10]

Sympathetic ophthalmia appears to respond to chlorambucil more readily than does Behçet's disease. Remission occurred in the patients with SO in our series with a lower total drug dose and a shorter duration of therapy than in those with Behçet's disease. This may reflect a difference in the ease of treating a systemic disease versus a localised eye disease or in the ocular status of our patients. None of our patients with SO had any extraocular manifestations. Alternatively, this difference may be an artefact caused by the small numbers of patients in our series.

Chlorambucil has serious side effects. The most dread potential side effect of chlorambucil is late malignancy, especially acute leukaemia or lymphoma. Most evidence indicates that the induction of leukaemia by chlorambucil is related to both duration of therapy and total past intake.[9,14] Kahn *et al*[22] reported 12 cases of leukaemia in 1612 patients with rheumatoid arthritis (0·75%) and four cases of leukaemia in 35 patients with psoriatic arthritis (11·4%) treated with chlorambucil. No cases of leukaemia were seen in patients treated for less than six months or with a total dose less than 1 g.[22] Most of the patients in whom leukaemia developed after chlorambucil therapy had received over one year of therapy and generally over 1·5 g of the drug.[9,22–28] To our knowledge the only case of leukaemia developing secondary to chlorambucil therapy with a total dose less than 1 g occurred in a 7-year-old girl who was treated with 300 mg of chlorambucil (15 mg/kg).[29] In addition several studies have reported an increased incidence of tumours in patients treated with chlorambucil.[30,31] Two of our patients exceeded the six-month period of therapy. All of our patients with Behçet's disease and two of the five patients with SO exceeded a total dose of 1 g. Malignancy has not yet developed in any of our patients (longest follow-up, 12 years).

Our finding that patients obtained sustained remission when the WBC or platelet levels remained depressed for about six weeks suggests a need to induce this toxic response. If we were to increase the dose of chlorambucil more rapidly, perhaps the total dose and duration of therapy might be further decreased and fewer side effects might occur. The paucity of patients with SO and Behçet's disease who qualify for this therapy makes it necessary to have collaborative trials of randomised drug regimens.

Because chlorambucil is an immosuppressive agent, a substantial number of viral, bacterial, and fungal infections as well as a 2% incidence of septicaemia and death have been reported in patients with rheumatoid arthritis treated with it long term.[32] Others have also reported infections accompanying long-term chlorambucil therapy.[3,29] Our patients have experienced no secondary infections while receiving chlorambucil.

Chlorambucil has also been reported to depress sperm counts and to inhibit the development of male secondary sexual characteristics.[10,11,33-36] Total chlorambucil doses less than 7·0 to 8·2 mg/kg in children[11,33] and 400 mg[34] of 6·1 mg/kg[35] in adults are believed not to affect fertility. Recovery of spermatogenesis has been noted by some[36] but not all investigators.[10,11]

The potential problem of male sterility makes it crucial to obtain informed consent. We inform our male patients of these findings and suggest to those who want children that they have sperm placed in a sperm bank in case they are sterilised by the drug. One 17-year-old patient in our series chose to place his sperm in a bank before beginning chlorambucil therapy. Artificial insemination after cryopreservation of semen in men with testicular tumours or Hodgkin's disease has been reported to result in a pregnancy rate of 45% at six months, compared with a usual cumulative probability of pregnancy of 71%.[37] One pregnancy occurred from semen that had been stored for 6·5 years.[37] We have no follow-up on the actual fertility of our male patients.

Little has been written about the effect of chlorambucil on women. Girls and women treated with chlorambucil for renal disease and malignancy have had normal children and normal levels of oestradiol, follicle stimulating hormone, and lutenising hormone,[33,38] though chlorambucil in combination with other chemotherapeutic agents can cause gross histological distruption of the ovaries and amenorrhoea.[39,40] Care must be taken that patients are not or do not become pregnant during therapy because of the possibility of teratogenic effects.[41,42] One of our patients who became pregnant after terminating chlorambucil therapy had a normal delivery and child.

Other serious side effects of chlorambucil are rare and usually occur after long-term therapy (over several years) with multiple dose regimens. These side effects include myelofibrosis,[43] bone marrow failure,[44] rashes,[45] and pulmonary fibrosis.[46] None of our patients has experienced these side effects.

For the previously stated reasons, chlorambucil should be used only in those patients for whom blindness is a real possibility without therapy. Prolonged follow-up may be necessary to understand fully the risks of chlorambucil.

Despite potential side effects chlorambucil has several advantages over other agents that might be used to treat SO or Behçet's disease. Cyclophosphamide, an alkylating agent closely related to chlorambucil, is also used to treat nonmalignant inflammatory diseases such as Wegener's granulomatosis and nephritis. However, because of its more rapid action, cyclophosphamide may be a more difficult drug to administer than chlorambucil,[18,47] and toxic effects may occur more rapidly than with chlorambucil. Sister chromatid exchange, a sign of chromosome damage, is greater with cyclophosphamide than chlorambucil.[48] Cyclophosphamide is also a teratogenic agent.[49] Furthermore, cyclophosphamide can cause male and female sterility,[49] haemorrhagic cystitis,[49] and bladder carcinoma,[50] possibly due to renal excretion of active metabolites.[49,51] Patients receiving cyclophosphamide require vigorous hydration to limit the bladder damage. Cystitis and bladder cancer are not associated with chlorambucil therapy.

Cyclosporin, a newer immunosuppressive agent, has been recently used to treat uveitis.[52-54] In one study nine patients with refractory posterior uveitis were given systemic cyclosporin. All patients had an improved visual acuity, a reduced corticosteroid dose, and decreased inflammation. However, in seven patients, cyclosporin-induced renal toxicity necessitated a reduction in dose, which led to a relapse of the uveitis.[52] Other reports indicated a need to taper the cyclosporin dose because of nephrotoxocity and to add systemic corticosteroids to the regimen to suppress inflammation.[54] A recent monograph emphasises the frequent need to use corticosteroids with low-dose cyclosporin.[55] Relapses of cases of Behçet's disease after discontinuing cyclosporin are reported.[56] These results indicate that cyclosporin suppresses inflammation but does not cause a long-term remission. Terminating cyclosporin therapy frequently results in rebound inflammation.[57] This is in contradistinction to the results with our regimen of chlorambucil, in which terminating chlorambucil therapy when toxicity was reached resulted in sustained remission of inflammation. Patients with severe uveitis appear to need long-term cyclosporin therapy, which has been associated with renal toxicity[57] and lymphoma.[58] Our experience with chlorambucil has necessitated only short-term therapy.

In summary, we have found chlorambucil to be useful in selected cases of SO and Behçet's disease. By using a technique of high-dose short-term therapy we could discontinue the use of systemic corticosteroids, place our patients into sustained remission, and theoretically reduce the side effects of chlorambucil. Thus we achieved our aim of eliminating side effects of long-term corticosteroids in addition to discontinuing all systemic medications within a relatively short period.

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# Contrast sensitivity function and pituitary adenoma: a study of 40 cases

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## Abstract

**The authors studied the contrast sensitivity function in 40 patients with pituitary adenoma. It seems to be a good index of compression of the visual pathway in this disease, but it lacks specificity and it cannot be used alone.**

There are few studies using contrast sensitivity function (CS) in pituitary adenoma (PA).[1-3] Usually associated with defects of the visual field, the alteration of CS may be total[1] or limited to low and middle spatial frequencies only.[2 3] We investigated such patients to determine whether loss of contrast sensitivity might be an early and sensitive index of compression of the visual pathway.

## Patients and methods

We reviewed the CS of 40 patients aged from 15 to 48 years suffering from PA (12 microadenomas <10 mm; 28 macroadenomas ⩾10 mm). We used stationary vertical sinusoidal gratings on a television screen with a technique described elsewhere.[4] Six spatial frequencies between 0·8 and 26 cycles per degree were presented. The mean of three determinations at each spatial frequency was compared with those of control subjects matched for age. Every value inferior to 2·5 standard deviation (SD) from the control population was considered to be pathological ($p<0{\cdot}01$). The results were compared visual acuity (VA) data, visual field (VF) data (Goldmann kinetic perimetry and/or automatic static central perimetry performed on a Vision Monitor system), and with the degree of expansion of the tumour, as measured by CT scan and surgical findings.

## Results

The CS was altered in 21 out of 40 cases of pituitary adenoma. The patients could be separated into three groups with respect to CS:

*Group I:* normal CS (n=19). The VA was equal or superior to 20/25. Ten patients had intrasellar microadenomas; nine were macroadenomas with an extrasellar expansion but only one extended upwards, bulging the optic chiasm. The visual field was also normal in 13 cases but abnormal in 6 cases.

*Group II:* bilateral attenuation of CS (n=13). The VA was decreased at least for one eye in 12 out of 13 cases (VA ranging from 0 to 20/25). The CS was not tested in one eye of four patients because of the poor VA. Attenuation of CS was observed in nine eyes in the high and middle frequency range, in eight eyes in the high frequency only, and was global in five eyes. The tumours were larger than in group I. Two were microadenomas and 11 were macroadenomas with suprasellar development. All these patients but one had a bitemporal hemianopia.

*Group III:* unilateral attenuation of CS (n=8). The VA was superior or equal to 20/30 in all eyes but one. Attenuation of CS was observed in the high and middle frequency range in three cases, in the high frequency range only in two cases, and was global in two cases. The CS was not tested in one eye because of the poor VA. All the tumours of group III were macroadenomas. The visual field was altered in five cases. In three patients whose CS was altered and visual field remained normal the tumour bulged upwards moderately through the diaphragma sellae.

## Discussion

Loss of CS is usually associated with alteration of VA and visual field. In small intrasellar adenomas the CS, VA, and visual field are normal. Bilateral attenuation of CS corresponds to profound alteration of VA and bitemporal hemianopia frequently found with the largest tumours. Unilateral alteration of CS corresponds to miscellaneous conditions, and the CS may be altered even though the visual field remains normal. In three cases, attenuation of CS was observed without other signs. In these cases the CS may provide an early sign of upward development of a pituitary adenoma.

On the other hand, in group I the visual field was altered in six cases even though CS remained normal (three were microadenomas, three were macroadenomas). The discrepancies observed in these tests suggest that it is useful to compare CS and VF when investigating patients with pituitary adenomas.

In conclusion, CS seems to be a sensitive index of compression of the visual pathway in PA. However, alteration of this measurement alone is not diagnostic because of its lack of specificity. Its usefulness is limited to the follow-up in association with study of the visual field.

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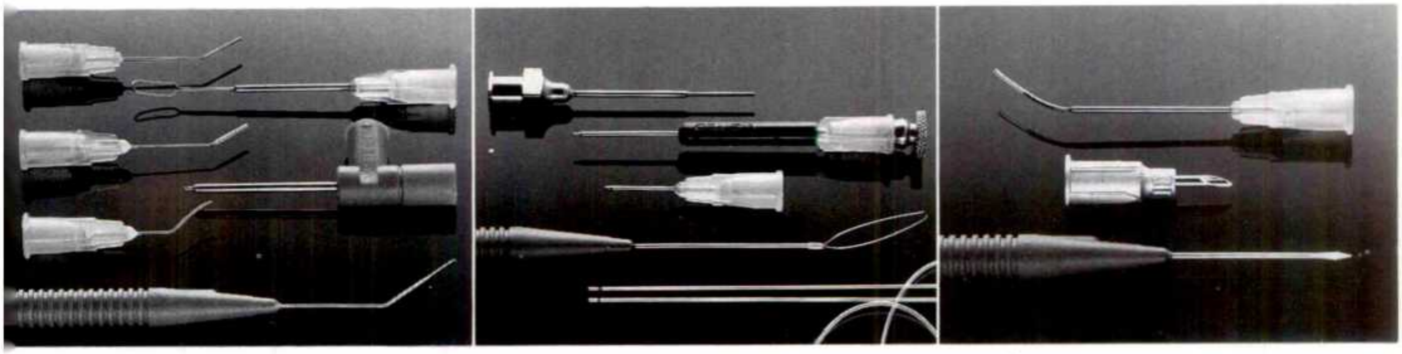

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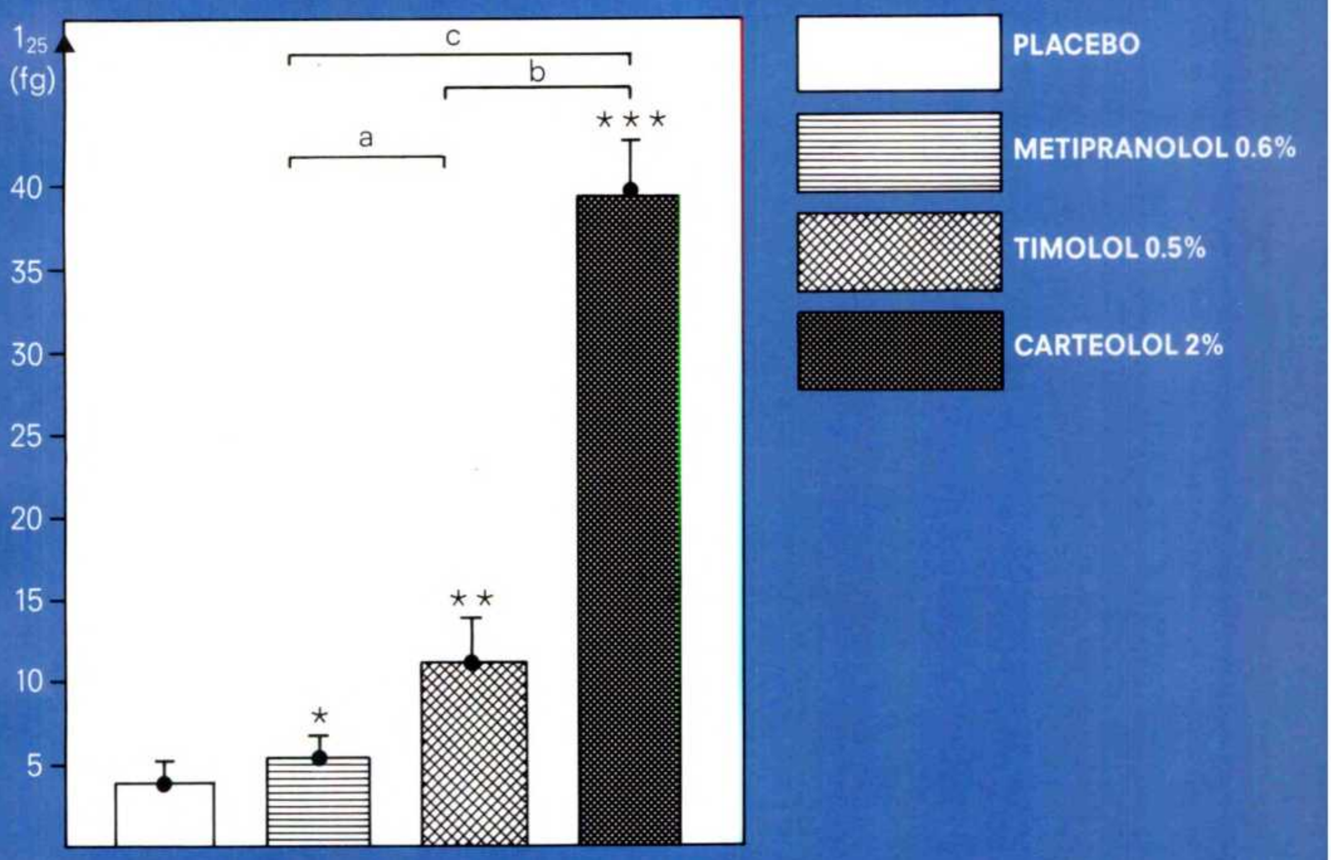

Dose of isoproterenol hydrochloride (mean ± SE) required to increase resting heart rate by 25 bpm ($I_{25}$) 3 hours after one drop of ophthalmic ß-blocker in each eye. (*$P < 0.05$; **$P < 0.001$; ***$P < 0.0005$ vs. placebo; a, $P < 0.02$; b, $P < 0.001$; c, $P < 0.001$.)

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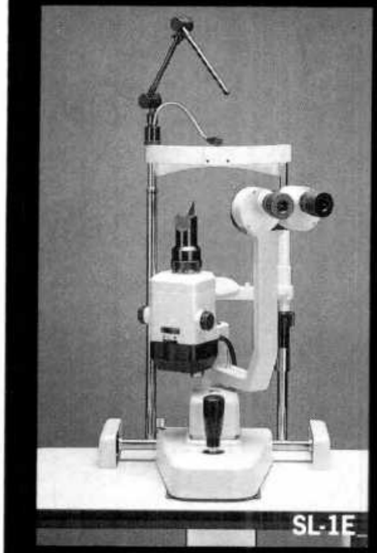

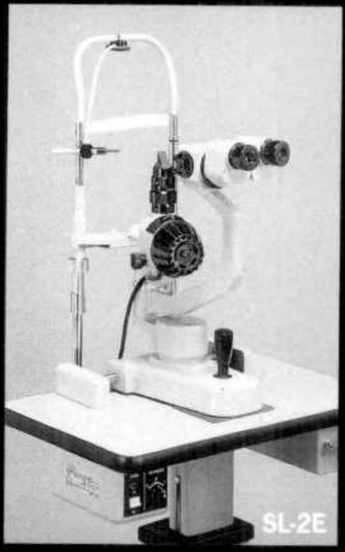

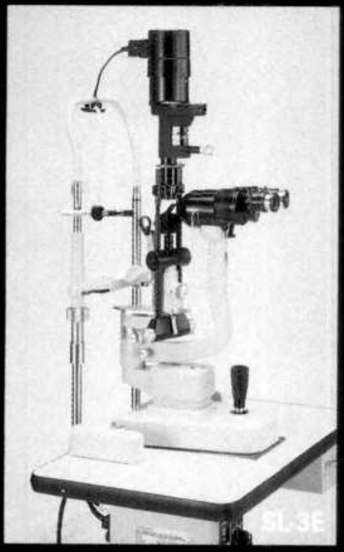

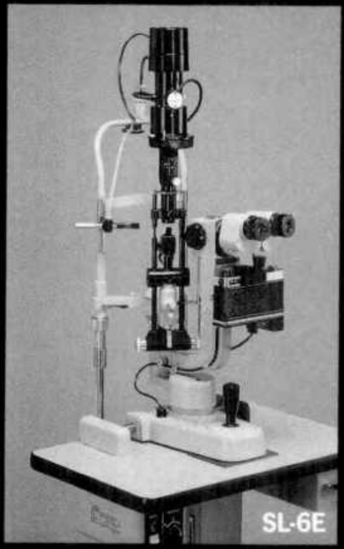

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*British Journal of Ophthalmology*, 1990, **74**, 359-362

# Changes in height of choroidal melanomas after plaque therapy

David H Abramson, Camille A Servodidio, Beryl McCormick, Daniel Fass, Edith Zang

## Abstract

**Serial ultrasonic measurements of 82 uveal melanomas treated with brachytherapy plaques (cobalt-60 and iodine-125) and followed up for up to 141 months revealed that no two patients had identical patterns of change. The mean absolute change in tumour height after treatment was 1·8 mm at six months, 5·6 mm at 48 months for large tumours, and 0·9 and 1·9 mm for medium sized tumours. Eighty of the 82 patients fell into one of three patterns of response: 57 patients had a decrease in height after treatment (type D), 13 patients had the same height after treatment (type S), and 10 patients had a progressive increase in height (type I). Life table comparison showed no correlation between survival and location of tumour, sex of patient, size of tumour when treated, or laterality. There was a slight correlation between age and survival. Patients older than 60 died more frequently from metastatic melanoma than those under 60 (p=0·06). Life table analysis showed a significant correlation between tumour regression type and survival. At 48 months the best cumulative probability of survival was in patients with type D (88% alive) compared with those of type I (34% alive, p=0·0004).**

Since Stallard's pioneering work scleral radioactive applicators (brachytherapy) has been used in many ways throughout the world. Cobalt-60, iodine-125, iridium-192, and ruthenium-106 have been used. Remarkably little is known about what happens to the ocular tumour in the eye after brachytherapy. Stallard[1] reported that the majority of melanomas he treated became flat; few other workers have achieved that result. Cruess *et al* calculated that a 'mean' change in tumour thickness was 20% reduction at six months, 30% at 12 months, and then a progressive decrease of 50% at 54 months. They concluded that the average posterior uveal melanoma treated with cobalt-60 did *not* regress to a flat scar and that the 'extent and rate of regression' were not reliable indicators of the patient's likelihood of developing metastatic disease.[2]

In the only other series that has been similarly analysed Coleman *et al* (New York) reported that tumour thickness was not a significant predictor of percentage reduction in height. However, they showed that ultrasonically derived spectral parameters did correlate with regression.[3] At six months they found that acoustic tissue type (ATT) B had a 29·5% reduction in height, while ATT E had an 11·4% reduction in height. At 18 months ATT B had a 53·9% reduction in height, while ATT E had a 26·4% reduction in height.

One of the authors of the present paper (DHA) involved in plaque therapy for two decades observed that these papers simplify data and represent an 'average response' that does not agree with all clinical observations. An average response does not accurately reflect what actually happens to ocular tumours after brachytherapy. This could be confusing to a clinician unfamiliar with the responses of treated tumours. Furthermore, there has been little comment in the literature about tumours in the eye that progress after plaque therapy and their significance for the eye and the patient. To answer these questions we retrospectively analysed the tumour height of plaqued melanomas in a series of patients diagnosed by DHA and treated with BM and DF. Follow-up data were available for up to 12 years.

## Material and methods

A retrospective analysis of 83 patients with uveal melanoma treated by one of us (DHA) was performed. The diagnosis of uveal melanoma was made in the usual way by ophthalmoscopy, fluorescein angiography, ultrasonography, and quantative echography, visual fields, and transillumination. The $^{32}$P test was done on two patients. No patient had received any prior therapy or a fine needle biopsy. Before treatment all patients were examined for metastastases, and none had been reported for any patient.

Ultrasonic heights of tumours were measured at most follow-up visits. To simplify the groups, plots have been performed at monthly intervals. If the patient had not actually been measured at that time, a mathematical weighted average was made between the two listed visits and this 'averaged' number was used for plotting data. Because of the technical problems associated with repeated ultrasonic measurements, we defined changes in height as subsequent measurements greater than 15% of the original measurement. Occasionally no ultrasonic measurements were performed, and the clinical estimate of the height was used for that visit. One patient was lost to follow-up.

Metastatic disease was detected by liver function tests, liver spleen scans, needle biopsies (of liver), bone scans, CT scans, magnetic resonance imaging (MRI) scans, and in some cases necropsy.

### STATISTICAL METHODS

The putative association between pairs of categorical variables was analysed through contingency tables and the $\chi^2$ statistic. Continuously measured characteristics such as age and tumour size were correlated by the Pearson product moment correlation technique, and the statisti-

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TABLE I *Results of treatment*

| I. | *Patients treated (83)* | | | | *Age* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *OD* | *OS* | *Male* | *Female* | *20–29* | *30–39* | *40–49* | *50–59* | *60–69* | *70–79* | *80–89* |
| Number: | 51 | 32 | 53 | 30 | 4 | 5 | 4 | 13 | 30 | 19 | 7 |

| II. | *Tumours treated (83)* | | | *Tumour vertex* | | | |
|---|---|---|---|---|---|---|---|
| | *Small* (2·0 mm- 3·0 mm) | *Medium* (3·1 mm- 8·0 mm) | *Large* (8·1 mm- 16 mm) | *Ciliary body* | *Anterior equator* | *Equator* | *Posterior equator* |
| | | | | 8 | 14 | 8 | 53 |
| | 4 | 63 | 16 | *Cobalt-60* | *Iodine-125* | | |
| | | | | 55 | 28 | | |

| *Pairs of variables* | *Correlation coefficient (R)* | *p Value* (t *test*) |
|---|---|---|
| Age vs tumour height before treatment | −0·009 | 0·93 NS |
| Location vs tumour height before treatment | 0·15 | 0·17 NS |
| Age vs location | −0·04 | 0·74 NS |

cal significance of the correlation coefficients was tested by the *t* test to estimate the probability that $r \neq 0$.

Linear regression analysis was employed to test and quantify the linear component of the relationship between pre- versus post-treatment tumour size at one, two, and three years follow-up.

The relationship between tumour height at various times of follow-up and the change in tumour height following treatment versus age, survival status, and pretreatment tumour size was evaluated through analysis of covariance. In these models the post-treatment tumour height and the change in tumour height after treatment represented the dependent variable; pretreatment tumour category (small, medium, and large) and survival status were the categorical independent variables; and age was the covariate.

The correlation of various continuous and categorical patient characteristics with survival was analysed by the Cox regression model,[4] followed by the likelihood ratio test. For univariate survival we used the Kaplan-Meier product limit estimate,[5] and the statistical significance of the differences between survival distributions was tested through the logrank summary $\chi^2$ test.[6] The distribution of continuous variables was normalised whenever necessary to meet the assumption of specific analytical techniques.

## Results

Results are summarised in Table I.

TABLE II *Mean change in tumour height following treatment*

| *Pretreatment tumour size* | *Mean change (in mm) after treatment at* 6 *mo* | *12 mo* | *24 mo* | *48 mo* |
|---|---|---|---|---|
| I . Actual change (in mm) | | | | |
| Small | 0·1 | 0·1 | – | – |
| Medium | 0·9 | 1·4 | 0·8 | 1·9 |
| Large | 1·8 | 2·8 | 3·5 | 5·6 |
| Absolute decrease in height was most pronounced in large tumours. The average monthly decrease in height for the first 48 months was 0·5 for the large tumours and 0·2 mm for medium tumours | | | | |
| II. Percentage of pretreatment height | | | | |
| Small | 101 | 100 | – | – |
| Medium | 88 | 76 | 87 | 76 |
| Large | 86 | 77 | 71 | 49 |
| The percentage decrease in tumour height was most pronounced in large tumours | | | | |
| III. Monthly actual change (average) | | | | |
| Small | 0·1 | 0·01 | – | – |
| Medium | 0·07 | 0·12 | 0·07 | 0·2 |
| Large | 0·1 | 0·23 | 0·3 | 0·5 |

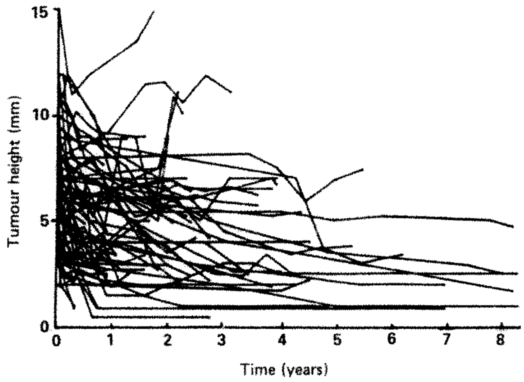

*Figure 1: Changes in height of tumours in each of the 83 patients.*

PATTERNS OF CHANGE AND METASTASES

The changes in tumour height over time are plotted in Figure 1, and see Table II. No two tumours had exactly the same pattern of change, but the changes did fall into one of four categories we have called type D (for net decrease in height; 57/82), type S (for same size after treatment; 13/82), type I (for net increase in height; 10/82), and type M (for miscellaneous; 2/82). One patient was lost to follow-up.

*Type D.* This pattern is characterised by a progressive diminution in tumour height immediately after therapy (Fig 2). In some cases the tumours remained stationary after shrinking and then shrank again. The maximal shrinkage seen was 8·1 mm in 29 months. In cases where the tumour diminished in size after reaching a plateau, the second regression began eight to 60 months after treatment. In these cases the magnitude of change was occasionally dramatic. One patient's tumour shrank 3 mm in two

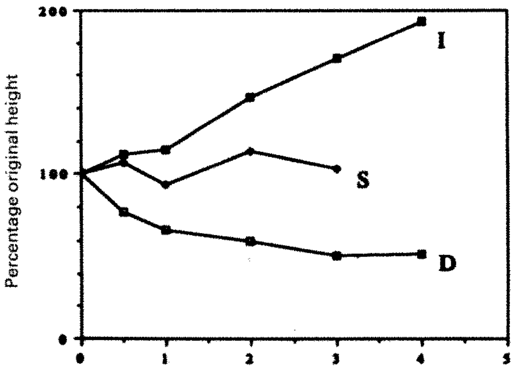

*Figure 2: Percentage changes (normalised) for each of the three post-treatment types.*

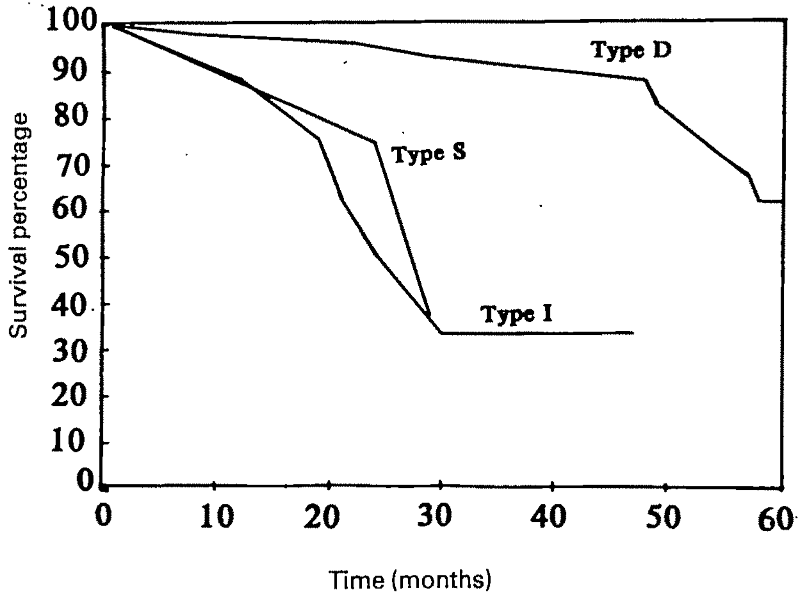

*Figure 3: Life table analysis of survival for patients by tumour type.*

months (from 15 mm to 12 mm), then remained stationary for seven months, and then shrank an additional 6 mm in six months. Another shrank 5 mm in two months, remained the same for 12 months, shrank an additional 2 mm over 35 months, and then remained the same for 81 months. The regression in height has been observed to continue for as long as 46 months after treatment. Seven of these patients developed metastases at 8, 22, 29, 48, 49, 54, and 58 months.

*Type S.* This pattern is characterised by a less than 15% change in height following treatment (Fig 2). One patient developed metastases 28 months after treatment.

*Type I.* This pattern is characterised by a progressive increase in size after plaque therapy (Fig 2). In these cases metastases occurred at 10, 21, 24, 27, and 30 months after treatment.

*Type M.* This miscellaneous group includes two patients in whom tumours remained the same for 8 and 15 months and then grew. One of these developed metastases at 26 months, and the other is alive 37 months after treatment.

### PATIENT SURVIVAL

The following features did not correlate significantly with survival: location of tumour, sex of patient, size of tumour prior to treatment, and laterality of eye.

*Age.* There was a significant correlation between age and survival. Patients who were older than 60 did less well than those who were 60 or younger ($p=0·06$).

*Regression pattern.* The life table analysis of survival for patients whose tumours either increased in size (type I), or remained the same (type S) was significantly different in comparison with those whose tumours decreased in size (type D) (Fig 3). Tumour height at 12 months did not differ significantly between those who survived and those who died.

## Discussion

The results of this study of changes in tumour height after plaque radiotherapy for choroidal melanomas agree with those of some prior studies, disagree with some observations of other investigators, and may prove to be a useful classification which clinicians can use as a guideline in following up patients.

What happens to the size of uveal melanomas after plaque treatment? Although Stallard[1] reported that the majority (70%) of melanomas he treated with cobalt-60 plaques became 'flat pigmented stippled' scars, he did not describe the time course of these changes. His observations were not made with the aid of ultrasonography and were largely based on the height measurement made with the direct ophthalmoscope.

Bedford, reporting on Stallard's cases and his own, noted that regression was frequently not complete for 1½ to 2 years after therapy.[7] Long *et al*[8] also demonstrated that melanomas treated with cobalt-60 plaques showed little, if any, changes for four to six months after treatment.

Most of the recent observations on this subject come from two institutions. From Cornell, Coleman *et al* found that tumours showed a progressive diminution of height (measured by ultrasound) at 6, 12, and 18 months after treatment and that this magnitude of change was 53·9% for ATT B and 26·4% for ATT E at 18 months.[3]

In 1984 Cruess *et al*,[2] reporting from the Wills Eye Hospital on their first 100 patients with uveal melanomas treated with cobalt-60 plaques, found that the 'average' posterior uveal melanoma did 'not regress rapidly to a flat, depigmented scar' but 'shrank slowly' to 50% of the thickness of the original tumour after 54 months. In the same paper the authors pointed out that there was no change in the maximal or minimal basal diameter of the tumour during 54 months of follow-up.[2] Additional analysis of the same 100 patients revealed that 96% showed a regression and that only three melanomas increased in thickness after therapy.[9]

In another analysis of 17 patients from Wills who were followed up for at least three months the post-treatment rate of decrease in tumour thickness (%/month) varied between 1·2 and 10·5. In no patient did the tumour grow after plaque therapy.[10]

We found that the mean post-treatment rate of decrease in large tumour thickness was: 2·3%/month in the first six months, 1·5%/month in the second six months, 0·5%/month in the second year, and 0·9%/month between year 2 and year 4. The changes for medium tumours were 1%, 2%, 0·75%, and 0·45% respectively.

The largest series published in which ultrasonic measurements were made was also from Wills, with an analysis of 159 patients treated between 1976 and 1980. In this series the prognostic value of the regression rate was studied.[11]

Our results generally agree with those of all the prior studies but have important features not discussed by others. We found that both the absolute and percentage decrease in tumour height were most pronounced in the large tumours and that the decrease in height tends to level off after 30 months. The average monthly decrease in tumour height for the first 48 months was 0·5 mm for large and 0·2 mm for medium tumours. The mean absolute change in tumour height after treatment in large tumours was 1·8 mm at six months and 5·5 mm at 48 months. For medium sized tumours these means are 0·9 mm and 1·9 mm respectively. When we actually superimposed each of the individual tumour responses, we could not find two tumours with exactly the same magnitude and time changes (Fig 1). This emphasises the individual responses of these tumours and should make clinicians wary of any discussion of 'average' changes.

When we looked for trends in height changes, we found that 80 of the 82 tumours fell into three categories. The most common (57 out of 82) of these was a progressive decrease in height after treatment (type D). The maximal shrinkage seen in this group was 8·1 mm in 29 months. In some patients the tumour got smaller, then remained stationary, and then finally shrank again 8 to 60 months after treatment. Only longer follow-up will reveal what ultimately happens to the size of these tumours.

The next commonest pattern seen was one where the tumour showed no response or remained exactly the same height following treatment (type S). These patients have been followed up for as long as 29 months. It is not known whether the tumour will eventually shrink or grow.

The least common, but perhaps the most important group, are those tumours which progressively increased in height (type I) after treatment. This increase continued until metastasis occurred, which is true for 5 out of 10 patients with this type to date.

We found that age was an important predictor of survival. Patients older than 60 did less well than patients under 60 when analysed in a multivariate fashion. This is a feature which has previously been reported by others and deserves re-emphasis.

It was of great interest that the three radiation regression patterns correlated with the development of metastasis, in contrast to the prior data from Wills. At four years of follow-up a life table analysis showed more than 66% with type I were dead versus 12% with type D. In 1984 the Wills group reported that the 'rate and extent of regression of posterior uveal melanomas following cobalt-60 plaque radiotherapy are poor indicators of the . . . subsequent development of clinical metastatic disease'. This was based on the first 100 patients treated there.

A further analysis of 159 patients from the same institution has been widely interpreted as showing that the tumours which most rapidly regressed have a greater chance of developing clinical metastasis.[11] In reality these authors showed that with univariate Cox modelling only the basal diameter at treatment correlated with survival (the larger the basal diameter, the greater the chance of developing metastasis). When multivariate Cox analysis was done, the most satisfactory model was one where the pretreatment basal diameter and the tumour thickness at 12 months after radiation were used.[11] Neither the Wills study nor this one showed a correlation with survival when the percentage change in tumour thickness was studied at 3 months, 6 months, or 12 months after treatment.

While we believe that the local response to therapy does correlate with survival and that the patients who develop metastasis are more likely to be those whose tumour grows after therapy, we emphasise that clinical metastases also develop in patients in whom the tumour remains the same or decreased after plaque therapy. Preventing growth of the tumour may be defined as 'local control' but does not necessarily mean that no metastasis will develop. Similarly, a decrease in size of the eye tumour may be associated with the clinical development of metastasis.

There may be many reasons for the failure of a plaque to cause tumour regression. Some of those reasons may be known at the present time while others may not. Geographic 'miss', or poor placement of the plaque, low dose or dose rate, and the presence of radiation-insensitive cells may be among them. Since enucleation of melanomas has been implicated as a causative factor for the development of metastasis, it should be mentioned that of nine patients whose tumours grew after plaque therapy, seven whose eye was enucleated died, while two who refused enucleation also died.

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*British Journal of Ophthalmology*, 1990, 74, 363-367

# Gyrate atrophy of the choroid and retina: ERG of the neural retina and the pigment epithelium

Christina Raitta, Synnöve Carlson, Kaarina Vannas-Sulonen

## Abstract

**The function of the neural retina and the pigment epithelium in 10 patients with gyrate atrophy was examined by the conventional alternating current electroretinogram and by direct current electroretinography to study the c-wave. The a- and b-wave responses were subnormal in all patients and the ERG was undetectable in patients with an advanced stage of the disease. The c-wave was recordable by the DC ERG from three patients with a less advanced stage of the disease. In one patient the c-wave could be recorded only from the other eye but the a- and b-wave responses were recordable in both his eyes.**

TABLE I *Age and sex distribution, visual acuity, and stage of disease and cataract of the GA patients*

| | | | | *Vision* | | *Cataract* | |
|---|---|---|---|---|---|---|---|
| *Case* | *Age* | *Sex* | *GA stage* | *OD* | *OS* | *OD* | *OS* |
| 1 | 7 | F | I | 0·6 | 0·7 | – | – |
| 2 | 12 | F | I | 0·8 | 0·7 | Central opacity | |
| 3 | 14 | F | I–II | 0·7 | 0·4 | Small opacity | |
| 4 | 16 | M | I–II | 0·5 | 0·2 | – | – |
| 5 | 21 | M | I | 0·8 | 0·6 | – | – |
| 6 | 36 | M | III | 0·2 | 0·2 | Aphakia | |
| 7 | 37 | M | IV | 0·25 | 0·3 | Aphakia | |
| 8 | 38 | F | II–III | 0·2 | 0·3 | Aphakia | |
| 9 | 41 | F | IV | 0·2 | 0·2 | Aphakia | |
| 10 | 46 | M | II | 0·6 | 0·4 | Posterior opacity | |

Grading[10]: Stage I: Round, separate, or fused atrophic areas in the midperiphery of the fundus. Stage II: Fused atrophic areas approaching the posterior pole. Stage III: A large degenerative area round the disc. Stage IV: all the posterior pole except the macula are atrophic.

Gyrate atrophy of the choroid and retina (GA) is a rare form of hereditary retinal dystrophy accompanied by a defect in ornithine metabolism.[1] The clinical opthalmological findings in GA include myopia, cataract, and chorioretinal degeneration. The metabolic defect presents as hyperornithinaemia, ornithuria, and deficiency of ornithine aminotransferase activity.[2] The human gene responsible for GA has been localised to chromosome 10.[3]

The full-field ERG has been shown to be reduced in amplitude at an early stage in GA patients,[4] and no normal ERG recordings have been reported in them.[5] Ophthalmoscopic and fluorescein angiographic findings of young patients suggest that the retinal pigment epithelium is affected early in the course of the disease.[4 6] One histological study on animals indicates that the primary changes in GA are located in the pigment epithelium.[7]

We studied 10 GA patients with a full-field flash ERG to establish the degree and cell level of the disturbance in the function of the neural retina. The c-wave of the ERG, which originates in the pigment epithelium,[9 10] was recorded by a direct current (DC) method.[8] The purpose of this study is to evaluate the function of the pigment epithelium as revealed by the ERG c-wave and to correlate these findings with the a- and b-waves of the conventional alternating current (AC) ERG in GA patients.

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## Material and methods

Ten GA patients, five females and five males, aged 7–46 years (mean 27 years) were studied. The results were compared with the recordings of eight normal subjects (aged 20–46 years, mean 31 years). The GA diagnosis was based on ophthalmoscopic findings, hyperornithinaemia, ornithuria, and established deficiency of the ornithine aminotransferase enzyme.[11] The latest plasma ornithine level of the patients was at 205–1300 μmol/l (mean 733 μmol/l, normal <70 μmol/l). The visual functions of the patients are summarised in Table I.

The subjects were dark adapted for 30 minutes before the ERG recording. The pupils were dilated with 0·5% tropicamide (Oftan Tropicamide) which produced a dilatation of 7–8 mm. The other eye was covered. The recordings were performed with the subjects supine. Both eyes were examined in the same session, the right eye first. There was an additional 15 min dark adaptation between the recordings of the two eyes.

A photostimulator (Grass PS22) with a xenon flash lamp was used. The duration of the flash was 10 μs and the maximum intensity 3·38 μJ/cm$^2$ at the eye level (measured with Model 350 Linear/Log Optometer with a photometric filter 21043, United Detector Technology). The stimulus light was attenuated with neutral density filters (Kodak). To obtain a near uniform illumination of the retina a full-field stimulator was used (LKC Systems Inc), which reduces the problems related to uncertain fixation.[12 13]

The recordings were performed with a disposable corneal wick electrode described by Sieving *et al*[14] and slightly modified by us. The recording method is described in detail elsewhere.[8] As no lid speculum was used, the subject was able to blink. The electrode was placed on the surface of the topically anaesthetised eye (0·4% oxybuprocaine hydrochloride, Oftan Obucain), where it settled above the margin of the lower lid. The electrode is well tolerated, and occasional blinking keeps it moist.

Beckmann's Ag-AgCl disk electrodes were used as ground (on the forehead) and reference (on the ipsilateral temple) electrodes. The preparations for the recording were performed in a darkened room with the help of a dim red slit-lamp (luminance 2 cd/m$^2$). The corneal potentials were amplified (amplification 1000) with an

TABLE II *The a- and b-wave implicit times and amplitudes of the GA patients and normal subjects*

| | *Patients* | | | *Controls* | | | *Student's t test* | |
|---|---|---|---|---|---|---|---|---|
| | *n* | *Mean (ms)* | *SD* | *n* | *Mean (ms)* | *SD* | *t* | *p* |
| IMPLICIT TIME | | | | | | | | |
| *a-Wave* | | | | | | | | |
| KW 47B+ND 0·6 | 11 | 29·3 | 4·1 | 11 | 27·7 | 0·72 | 1·27 | – |
| KW 25 | 11 | 17·9 | 2·8 | 11 | 16·3 | 0·47 | 1·86 | – |
| ND 1 | 11 | 19·9 | 4·4 | 11 | 17·0 | 0·44 | 2·18 | <0·05 |
| Bgr, KW 25 | 10 | 15·9 | 2·6 | 11 | 14·0 | 1·13 | 2·23 | <0·05 |
| Bgr, ND 1 | 10 | 15·9 | 2·0 | 11 | 14·6 | 0·98 | 1·90 | – |
| *b-Wave* | | | | | | | | |
| KW 47B+ND 2 | 10 | 85·5 | 9·9 | 11 | 81·9 | 4·1 | 1·10 | – |
| KW 47B+ND 0·6 | 11 | 54·6 | 6·6 | 11 | 51·1 | 2·1 | 1·48 | – |
| KW 25 | 11 | 51·6 | 3·9 | 11 | 52·7 | 1·5 | 0·87 | – |
| ND 1 | 11 | 45·5 | 7·3 | 11 | 43·0 | 3·1 | 1·05 | – |
| Bgr, KW 25 | 11 | 31·8 | 3·6 | 11 | 28·2 | 0·45 | 3·29 | <0·01 |
| Bgr, ND 1 | 11 | 29·7 | 2·9 | 11 | 27·3 | 0·72 | 2·64 | <0·05 |
| Flicker | 11 | 32·8 | 1·6 | 11 | 29·9 | 1·27 | 4·71 | <0·001 |
| | | | | | | | *Wilcoxon test* | |
| | *n* | *Med. (μV)* | *Range min/max* | *n* | *Med. (μV)* | *Range min/max* | *u* | *p* |
| AMPLITUDE | | | | | | | | |
| *a-Wave* | | | | | | | | |
| KW 47B+ND 0·6 | 11 | 3·5 | 3·5/42 | 11 | 63 | 46/101 | 3·94 | <0·001 |
| KW 25 | 11 | 17·5 | 3·5/49 | 11 | 45·5 | 32/81 | 3·84 | <0·001 |
| ND 1 | 11 | 38·5 | 3·5/119 | 11 | 136 | 88/220 | 3·74 | <0·001 |
| Bgr, KW 25 | 10 | 7·9 | 3·5/13 | 11 | 17·5 | 14/32 | 3·83 | <0·001 |
| Bgr, ND 1 | 10 | 9·4 | 1·8/28 | 11 | 21 | 15/35 | 3·17 | <0·001 |
| *b-Wave* | | | | | | | | |
| KW 47B+ND 2 | 10 | 40·2 | 21/74 | 11 | 157·0 | 95/220 | 3·83 | <0·001 |
| KW 47B+ND 0·6 | 11 | 49·0 | 28/154 | 11 | 213·0 | 147/329 | 3·87 | <0·001 |
| KW 25 | 11 | 45·5 | 18/175 | 11 | 248·0 | 147/413 | 3·84 | <0·001 |
| ND 1 | 11 | 38·5 | 18/108 | 11 | 157·0 | 84/325 | 3·81 | <0·001 |
| Bgr, KW 25 | 11 | 24·5 | 14/30 | 11 | 71·7 | 44/129 | 3·94 | <0·001 |
| Bgr, ND 1 | 11 | 32·5 | 6/49 | 11 | 96·2 | 51/140 | 3·94 | <0·001 |
| Flicker | 11 | 24·5 | 7/61 | 11 | 59·5 | 25/110 | 2·99 | <0·01 |

KW=Kodak Wratten. ND=neutral density. Bgr=background. n=Number of eyes.

AC/DC ERG amplifier (Biotronics, PO Box 29, SF-02421 Jorvas, Finland) and filtered (AC recording; low pass frequency 400 Hz, DC recording; low pass frequency 30 Hz). The recorded potentials were displayed on a digital oscilloscope (Gould 1425), which also provided the possibility for signal averaging. The implicit times (measured from the onset of the stimulus to the peak of the waves) and the amplitudes (measured from the baseline to the peak of the waves) were measured with a cursor. For the a-wave the earliest negative peak was measured. The waveforms were drawn from the oscilloscope with a pen recorder (Gould LS270) with a slow drawing speed (20 s/trace).

In the first recording session both eyes were studied for rod and cone mediated responses. Dark-adapted responses were elicited with the following test stimuli in the absence of a background illumination:

(1) Blue flash (KW47B, intensity 0·247×10$^{-1}$ μJ/cm$^2$) attenuated with neutral density filters to determine the b-wave threshold. (2) Blue flash (KW47B with 2·0 log units attenuation, intensity 0·195×10$^{-3}$ μJ/cm$^2$) to elicit a rod mediated response. (3) Blue flash (KW47B with 0·6 log unit attenuation, intensity 0·140×10$^{-1}$ μJ/cm$^2$) to elicit a rod mediated response. (4) Red flash (KW25, intensity 0·459 μJ/cm$^2$) to elicit a mixed cone and rod mediated response; the red stimulus and the previous blue stimulus (KW47B with 0·6 log unit attenuation) were matched subjectively to be equally strong stimuli for the rod system.[15] (5) White flash with 1·0 log unit attenuation (intensity 0·394 μJ/cm$^2$) to elicit a mixed cone and rod mediated response.

With a white background illumination in the globe (luminance 28 cd/m$^2$) the following test stimuli were presented to elicit cone mediated responses:

(1) Blue flash (KW47B with 0·6 log unit attenuation). With this stimulus no response was recordable in normal subjects, so that the same stimulus in the dark-adapted conditions elicited the response mainly from the rod system. This control test was performed only in normal subjects. (2) Red flash (KW25). (3) White flash with 1·0 log unit attenuation. (4) White 30 Hz flicker (intensity of the white flash 3·38 μJ/cm$^2$). The c-wave was recorded in a separate session.

The patient was prepared for the recording as described above. A DC recording method was used which enabled the recording of the slow c-wave. A small red fixation light was lit inside the globe to help the patient maintain fixation for several seconds. The subjects were instructed to avoid movement and blinking during several seconds after the stimulus. The stimulus was a white flash with 1·0 log unit attenuation (intensity 0·394 μJ/cm$^2$). A prestimulus time of 0·96 second was provided for the recordings by the recording system, and the response to each stimulus was recorded for 10 seconds. No signal averaging was used to avoid contamination of the recordings by occasional traces containing eye blinks or eye movements. Several single responses were recorded. All recordings were performed in the morning.

## Results

AC ERG was performed in both eyes of eight patients (cases 1–5, 7, 9, and 10). In two patients (cases 6 and 8) only one eye was studied because their other eye had recently been operated on for cataract. When a- and b-waves were undetectable, no c-wave recording was attempted (cases 6–9). Thus the DC ERG was performed on six patients (cases 1–5 and 10).

The AC ERG was isoelectric in both eyes of two patients (cases 7 and 9), in the recorded eye of cases 6 and 8, and in one eye of case 3. The b-wave threshold was raised in all patients with measurable responses.

The results of the a- and b-wave recordings of those GA patients whose ERG was not isoelectric are listed in Table II together with the results of the normal recordings. The implicit times of the a- and b-waves were slightly delayed in GA patients in comparison with normal subjects, but the difference was statistically significant only for the cone mediated responses (statistical analysis was by Student's *t* test for independent samples) (Table II). The implicit time of the a-wave was significantly delayed in GA patients in comparison with normal subjects also in one test for mixed rod and cone mediated response (white flash without background illumination). In all recordings of the GA patients the a- and b-wave amplitudes were reduced. The difference in results between the GA patients and normal subjects was also statistically significant (non-parametric Wilcoxon test for independent samples) (Table II). Figure 1 shows an example of the normal recording. The responses of three patients (cases 2, 4, and 8) are illustrated in Figure 2A, B, C.

*Figure 1: Normal AC ERG recording. From top to bottom: b-wave threshold (blue stimulus, KW 47B, ND 3·3, intensity 0·118× $10^{-4}$ μJ/cm²); rod mediated response (KW 47B, ND 2); rod mediated response (KW 47B, ND 0·6); mixed rod and cone mediated response (red stimulus, KW25); mixed rod and cone mediated response (white stimulus, ND 1); no response (see text) (white background illumination, 28 cd/m², and blue stimulus, KW 47B, ND 0·6); cone mediated response (white background illumination and red stimulus, KW 25), cone mediated response (white background illumination and white stimulis, ND 1); cone mediated response (white background illumination, 30 Hz white flicker, flash with no attenuation). Dashed line indicates the occurrence of the stimulus (duration 10 μs). Each recording is the average of four single responses. B=blue, R=red, W=white, bgr=background illumination.*

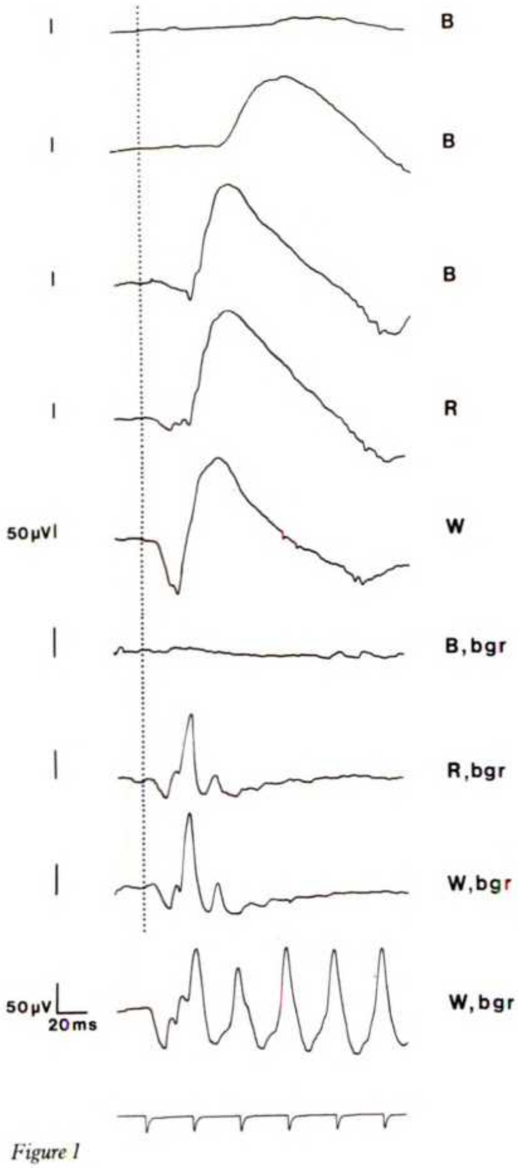

*Figure 1*

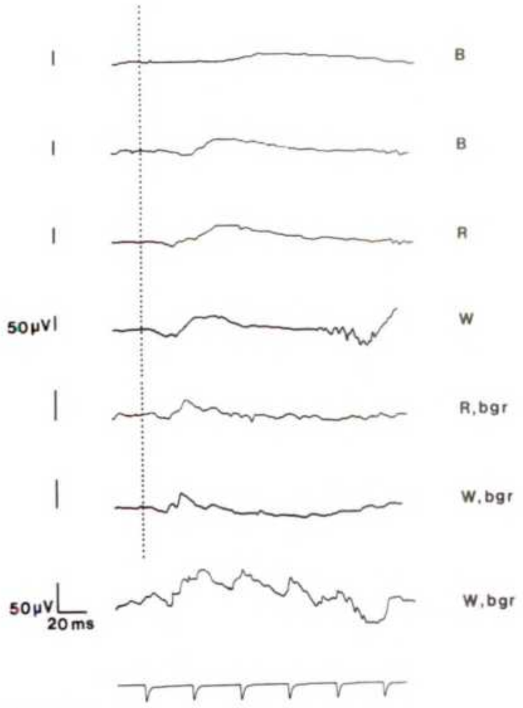

*Figure 2B*

The c-wave was recorded in six patients (cases 1–5 and 10). In one patient (case 1) the DC recording failed. This 7-year-old girl could not avoid moving the eyes during the recording. In one patient (case 2) the c-wave was recordable in both eyes (Fig 3). She was the second youngest (12 years) of the patients in this study. The clinical ophthalmological findings of her eyes corresponded to stage I in the grading described by Takki[16] (Fig 4). In the 16-year-old male (case 4) the c-wave was recordable from the right eye but not from the left (Fig 3). This finding was verified by repeating the recordings the following day. The clinical ophthalmological findings

*Figure 2: Flash ERG of three patients. A: A 16-year-old male (case 4), right eye. B: A 12-year-old girl (case 2), right eye. C: A 38-year-old woman (case 8). The stimuli from top to bottom: (1) blue (KW 47B, ND 2); (2) blue (KW 47B, ND 0.6); (3) red (KW 25); (4) white (ND 1); (5) white background illumination (28 cd/m²), red flash (KW 25); (6) white background illumination, white flash (ND 1); (7) white background illumination, 30 Hz white flicker, flash with no attenuation. Each recording is the average of four single responses. B= blue, R=red, W=white, bgr= background illumination.*

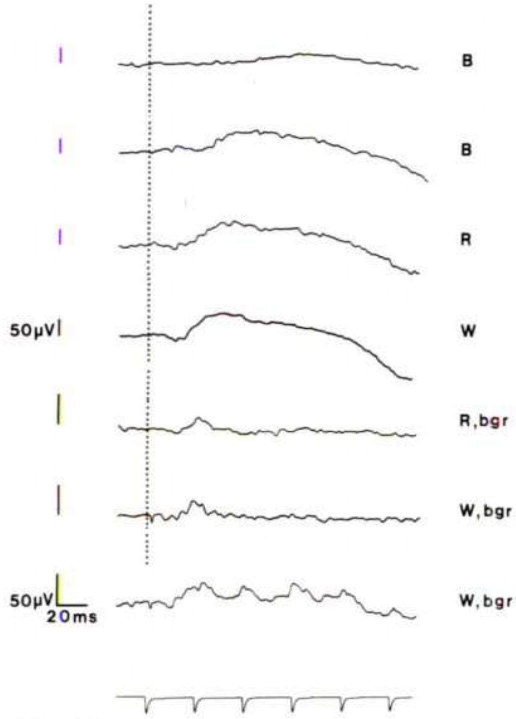

*Figure 2A*

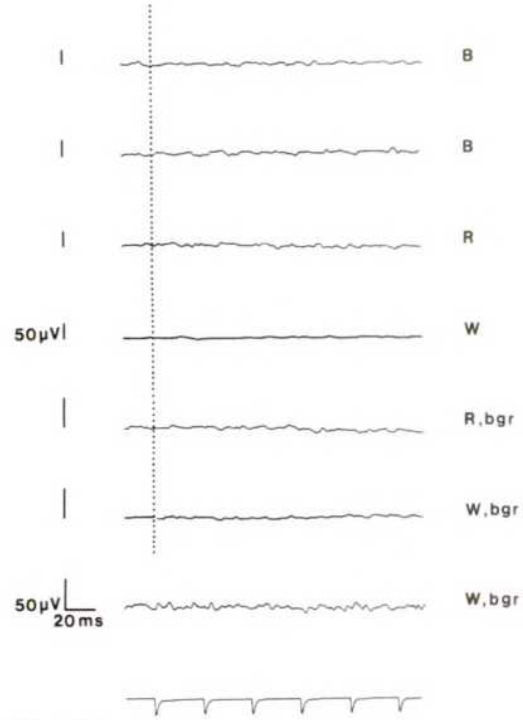

*Figure 2C*

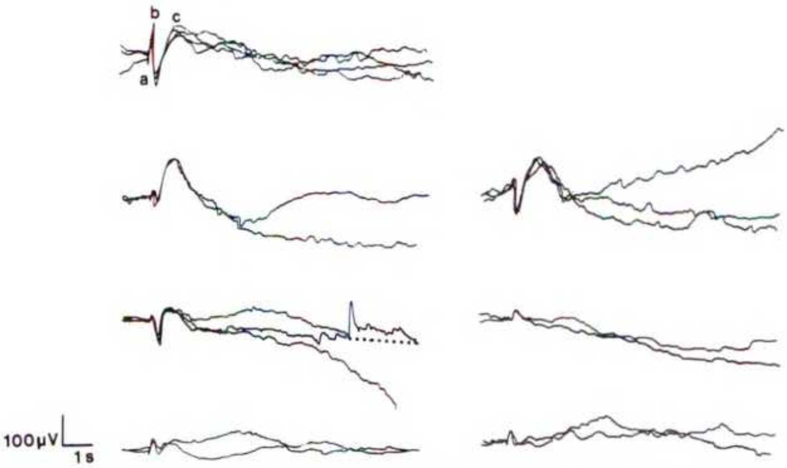

*Figure 3: Examples of the c-wave recordings. Top: Normal c-wave recording. Second: Case 2. C-waves were recordable in both eyes. Third: Case 4. C-wave was recordable in the right eye (left) but not in the left eye (right). Bottom: Case 10. A small positive deflection at a latency characteristic of the c-wave in the recordings from both eyes. The stimulus, a white flash with 1·0 log unit attenuation (duration 10 µs), was presented just before the occurrence of the a- and b-waves with a latency of 0·96 s from the beginning of the recording. Two to four responses are superimposed.*

TABLE III *Implicit time and amplitude of the c-wave in GA patients and in normal persons*

| | | *Implicit time (s)* | *Amplitude (µV)* |
|---|---|---|---|
| Case 2 | OD | 0·79 | 127 |
| | OS | 0·85 | 124 |
| Case 4 | OD | 0·79 | 98 |
| | OS | – | – |
| Case 10 | OD | 0·76 | 10 |
| | OS | 0·80 | 13 |
| Normal | n=9 | 0·90 0·08<br>(Mean) (SD) | 147 80<br>(Mean) (SD) |

of his eyes corresponded to stage I–II (Fig 5). A small positive deflection with an implicit time characteristic of the c-wave, was recorded from case 10 (stage II). In the other two patients (cases 3 and 5) no c-wave was recordable from either eye. The results of the c-wave recordings of the GA patients are listed in Table III together with the normal values.

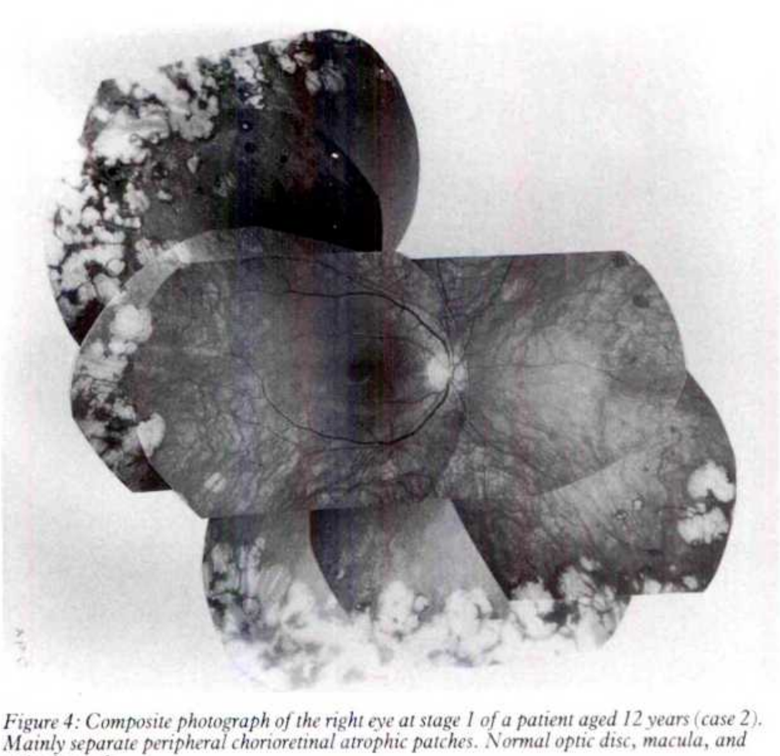

*Figure 4: Composite photograph of the right eye at stage 1 of a patient aged 12 years (case 2). Mainly separate peripheral chorioretinal atrophic patches. Normal optic disc, macula, and retinal vessels.*

## Discussion

The first detailed ophthalmological description of the characteristics of GA appeared in 1974.[16] Since then several reports on the electrophysiological findings in GA have recorded that the ERG is severely affected and may become undetectable at an early stage of the disease.[4 6 17-20] Typical for the disease is that its progress is variable and does not correlate with the age of the patients.[11 21]

In the present study the ERG was undetectable in patients whose clinical ophthalmological findings corresponded to GA stages II–IV (cases 3 and 6–9). The stage of the disease was less advanced in those patients who still had measurable responses in their ERG (cases 1–5 and 10). Both rod and cone mediated a- and b-wave amplitudes were decreased in the ERG of these patients, indicating that the rod and cone systems are affected jointly in GA. Of the two young patients described by Berson *et al*[18] one had a markedly depressed ERG with rod responses more reduced than cone responses. Kaiser-Kupfer *et al*[4] on the other hand did not report a difference in the degree of impairment of the two systems.

The c-wave was recordable in both eyes of the 12-year-old patient (case 2, stage I) of this study. In her AC ERG there was already a marked reduction in both cone and rod mediated responses. Of particular interest is case 4 (the 16-year-old male), in whose right eye the c-wave was still recordable but not in the left eye. The rod and cone mediated responses, however, were recordable in both eyes. In the DC ERG of case 10 (a 46-year-old male) a small positive deflection occurred in both eyes at a latency characteristic of the c-wave. The clinical picture of case 10 (stage II) indicates that his disease has progressed slowly and is an example of the heterogeneity of GA. The DC ERG findings of this study indicate that the c-wave can be recorded only at an early stage of the disease.

Since Noell's observation that the c-wave disappears after the pigment epithelium is selectively destroyed[9] several studies have supported the idea that the c-wave is in large part elicited by the pigment epithelium.[10 22] When retina is illuminated, there is a decrease in the extracellular levels of $K^+$ around the photoreceptors which gives rise to a hyperpolarisation of the apical membrane and to a less extent of the basal membrane of the pigment epithelium.[23]

The retinal pigment epithelium maintains the photoreceptor cell homoeostasis. The light sensitive disc membranes in the outer segments of the photoreceptor cells are renewed normally throughout life. This process involves multiple steps,[24] and a defect in one step may disturb the renewal mechanism and lead to cell abnormalities or cell death. The disappearance of the c-wave at an early stage of the disease is an indication of the disturbed function of the pigment epithelium.

To our knowledge this is the first time that any electrophysiological evidence of the function of the pigment epithelium in GA has been presented. The c-wave was detectable only in the early stages of the disease. In all patients with recordable c-waves the photoreceptor responses were subnormal. With clinical ERG it is not

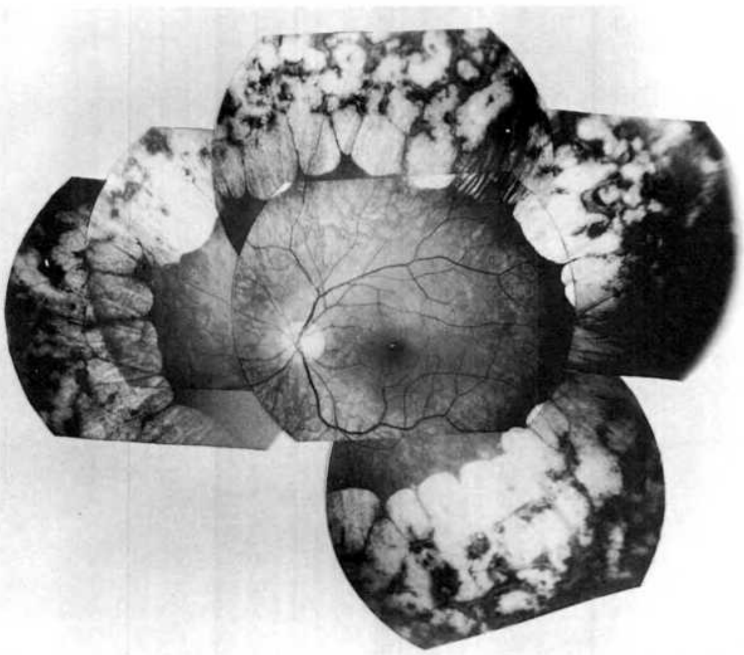

*Figure 5: Composite photograph of the left eye at stages 1–2 of a patient aged 16 years (case 4). Sharply demarcated confluent atrophic patches of garland shaped configuration. Normal optic disc and retinal vessels. Small pigmentary defect parafoveally in the left eye.*

possible to determine whether the pigment epithelium is affected earlier in GA than the neural retina. However, in case 4 the absence of the c-wave in the other eye, in which a- and b-waves were still recordable, may be an indication that the functional disturbance originates in the pigment epithelium.

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British Journal of Ophthalmology, 1990, 74, 368–369

MINI REVIEW

# Anterior segment surgery

This is a review of the most recent events in anterior segment surgery. Improvements are still being seen resulting from the general use of microsurgical instrumentation, viscoelastic agents, and finer suturing in the refinement of old and the introduction of new operative techniques. These, however, are well established,[1 2] so although fundamental to many advances they will not be mentioned further.

**Cataract surgery**

There is much active interest, even turmoil, in cataract surgery, with a plethora of new intraocular lens designs aiming at still greater advantage (and market edge). These include surface modification to reduce endothelial hazard, the use of soft materials to permit the insertion through a small incision, and multifocal lenses to increase the already remarkable number of patients who enjoy good close vision without an additional reading correction after lens implant surgery.

A method of accurate anterior capsulotomy (capsulorhexis) is being used to prevent accidental equatorial tears. This reduces the risk of decentration of the lenticulus, important in the use of multifocal and small diameter lenses.

Although there is discussion on the relative advantages of interrupted or continuous sutures, security of wound closure is now so well established that more attention can be given to the ultimate refractive error. There is much interest in small incision cataract surgery to reduce healing time and induced refractive errors. It may be thought that emmetropia would be desirable, but in fact a small myopic astigmatism has great advantages for patients after intraocular surgery.[3]

It is profoundly disturbing to hear reports that intraocular lenses already withdrawn in the United States are being promoted in the Third World, with resulting high incidence of endothelial dystrophy.[4]

**Corneal surgery**

Surgery for refractive errors continues to excite much interest, not only within the profession but also in the media and among the general public. There is a general understanding that ophthalmic surgery is more secure and successful than in the recent past. Thus, a patient who has to wear an awkward optical correction after surgery may consider the result something of a failure.[5] Surgeons continually strive to improve the results of their surgery, and more and more are inclined to undertake refractive surgery to achieve this end. In the knowledge that most patients obtain good visual acuity with spectacles or contact lenses, great care must be taken in the evaluation and practice of refractive surgery.[6-8]

There are more new instruments for the measurement of corneal topography by keratometry, keratophotography, and computer graphics. Much of this equipment is very expensive, but accurate surgical planning and execution are very necessary if there is to be progress towards more satisfactory and reliable results.

**Methods**

Methods of refractive surgery still include all the earlier concepts of treating visual defects by planned corneal surgery. They include keratomileusis (corneal sculpturing), keratophakia (intralamellar insertion of a lenticule of cornea or substitute material), wedge resection, radial keratotomy and other relaxing incisions, compression sutures, lamellar and penetrating corneal grafts, thermokeratoplasty, and, more recently epikeratophakia ('the living contact lens'). None of the methods are free of complication, and many involve cutting the normal cornea or removing a wedge from it. Such operations have irrevocable effects, and if the outcome is unsatisfactory they cannot be reversed. No surgical methods to alter refraction are fully predictable; they all have inaccuracies.

The predominant interest in the use of relaxing incisions has been for correction of myopic refractive errors. The quality of preoperative assessment and surgical technique is high, with great respect for the corneal endothelium. While long-term follow-up shows 75% of radial keratotomy results to be stable, 25% show increasing hyperopia. A similar proportion have fluctuating visual acuity.[9]

The current indications for donor epikeratoplasty are restricted, and there is research into a cheaper artificial material which will encourage early epithelial cover.[10]

**Astigmatism**

Although most refractive surgery has been performed for small or moderate degrees of myopia, it is patients suffering from high refractive errors who have the greatest clinical need for surgical relief. Seiler and others[6] correctly state that the primary corneal locus of astigmatism suggests that surgical intervention for astigmatism has a more pressing indication than other refractive errors, especially given the limited ability of spectacle or contact lens technology to compensate for large astigmatic errors. The increased interest in this subject is illustrated by the publication of one whole issue of a current journal devoted to articles on astigmatism only.[11]

Despite the efforts to close wounds accurately some patients end up with gross astigmatism in an otherwise good eye, and this usually proves to be due to inaccurate surgery. There are now many papers on the correction of graft astigmatism but very few on other surgically induced and traumatic astigmatism. It is carelessly suggested that such astigmatism can be reduced by removing all sutures, but this is not predictable, and often it can be made worse. A wound revision is often necessary.

At present the accuracy of prediction is not good enough to justify surgery for less than 6 dioptres of astigmatism, unless the symptoms are pressing. If the other eye has a similar astigmatism, but with an axis at right-angles the combined effect is used in assessment. The significant variability of effect is illustrated by the following examples.

Transverse (T)- cuts give an average correction of 6 dioptres of astigmatism, but with a standard deviation of 5·7 dioptres.[12] Markedly distorted mires have been reported after wedge resection for high postkeratoplasty astigmatism. One of 11 patients had increased astigmatism.[13] Methods of correcting astigmatism are still not consistent or predictable; results show a range from 3 to 23 dioptres of correction.

## The Future: laser refractive surgery?

It is expected that the excimer laser will have enormous potential in making more precise corneal incisions. If this results in less postoperative astigmatism after penetrating keratoplasty, more satisfactory visual results will be obtained.[14] Similarly great value could come from the accuracy of wound preparation in the whole range of anterior segment surgery. For example, glaucoma filtration could be established by taking an incision just deep enough to permit controlled aqueous escape without entering and decompressing the anterior chamber.

As mentioned above very recent developments with the excimer laser suggest that there are exciting developments on the horizon. Corneal laser surgery seems to be a highly precise procedure. The controlled and uniform depth of the excision leads to improved predictability of the refractive result. Various incision shapes can be programmed which may be more suitable for modifying the corneal topography than the linear and arc incisions currently used. If an area of Bowman's membrane is destroyed, a subepithelial stromal response is troublesome, and another development being investigated is laser ablation of the stroma under a flap, so that Bowman's membrane remains intact.[15]

We can be sure that, from all these areas of development, the prospects in anterior segment surgery will continue to be exciting during this decade.

M J ROPER-HALL

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CASE REPORTS

# Refsum's disease: electron microscopy of an iris biopsy

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**Abstract**

**Refsum's disease (phytanic acid storage disease) results in an accumulation of lipid as a result of an absence of mitochondrial hydroxylation of phytanic acid. We describe a previously unrecorded electron microscopic study of lipid deposition in the iris pigment epithelium of a patient with Refsum's disease, and lipid was present in other sites within the iris.**

Refsum's disease (heredopathica atactica polyneuritiformis[1,2]) is an autosomally recessive inherited absence of α hydroxylation of phytanic acid (3,7,11,15 tetramethyhexadecanoic acid), a breakdown product of chlorophyll found especially in dairy products. The disease is manifested by a chronic polyneuropathy and cerebellar ataxia with retinitis pigmentosa and a variety of other ocular signs (Table). Symptoms begin in the second or third decade with an insidious, occasionally remitting course.

Pathological reports on Refsum's disease have led to the findings of phytanic acid and lipid accumulation in the liver, kidneys, heart, and central nervous system.[3] Peripheral nerve studies show loss of myelinated nerve fibres with hypertrophy and 'onion bulb' whorls of Schwann cells[4] and perineural fibrosis. Phytanic acid in low concentrations has been recovered from peripheral nerves and in much higher concentrations from the retina and ciliary body.[5]

One necropsy report of the appearances within the eye showed complete loss of photoreceptors, thinning of the inner nuclear layer, and reduction in the number of ganglion cells of the retina.[6] Sudan III and Sudan black stains demonstrated lipid loading in retinal vessels. Lipid had also accumulated in the pigment epithelium of the retina, ciliary body, trabecular meshwork round the canal of Schlemm, and in both sphincter and dilator muscles of the iris, but not within the pigment epithelium in this case.[6]

## Case report

Iris of a 36-year-old man was obtained after an extracapsular cataract extraction and lens implant and broad iridectomy. A diagnosis of retinitis pigmentosa was made clinically 15 years ago after he had presented with night blindness and tunnel vision. There was no family history of the disease. Three years later he developed a mixed sensory-motor polyneuropathy. A raised serum phytanic acid and sural nerve biopsy confirmed the diagnosis of Refsum's disease.

TABLE *Ocular and non-ocular signs in Refsum's disease*

| *Ocular* | *Non-ocular* |
|---|---|
| Retinitis pigmentosa | Peripheral neuropathy |
| Cataracts | Cerebellar ataxia |
| Miosis | Deafness/anosmia |
| Ophthalmoplegia | Goitre |
| Ptosis | Ichthyosis |
| Glaucoma | Cardiomyopathy |

Ocular examination prior to surgery revealed visual acuities of 6/60 in both eyes, unreactive miosis, bilateral posterior subcapsular cataracts, and extensive 'bone-corpuscular' retinitis pigmentosa. The iris was fixed in formalin and glutaraldehyde and processed for light and electron microscopy.

## Results

Vacuoles of lipid, manifested by empty spaces, were visible in the biopsy. These were partic-

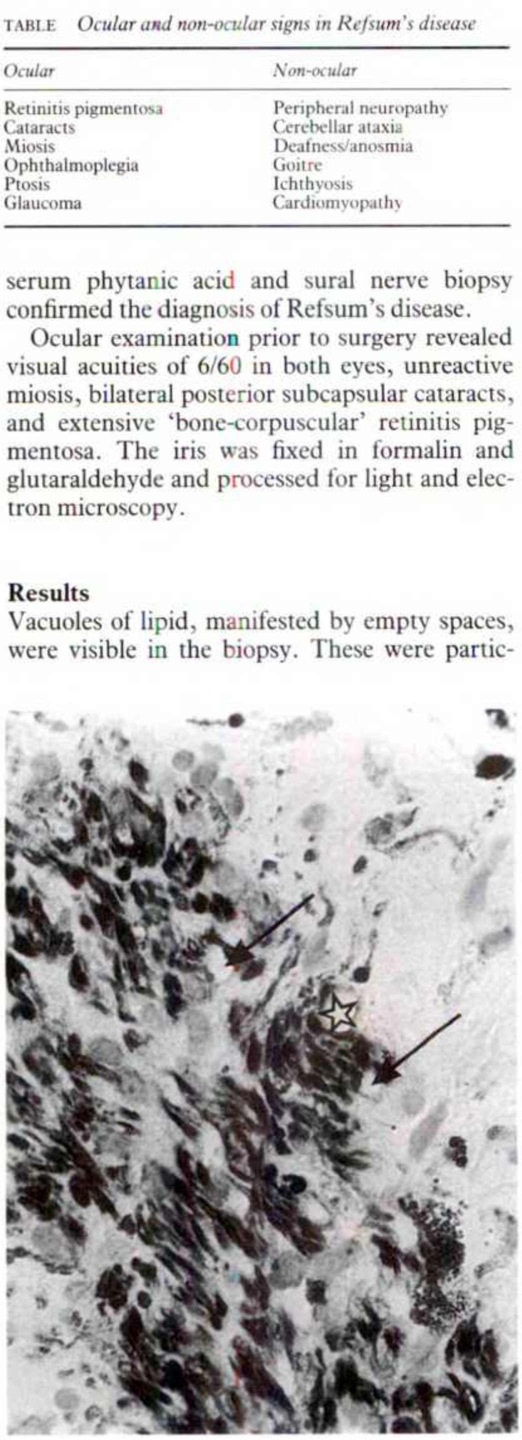

*Figure 1: Vacuoles of lipid (arrowed) dissolved out during processing, visible as spaces within the iris sphincter muscle, which is stained immunohistochemically with antibodies to desmin filaments; a capillary is indicated by the star. (×450.)*

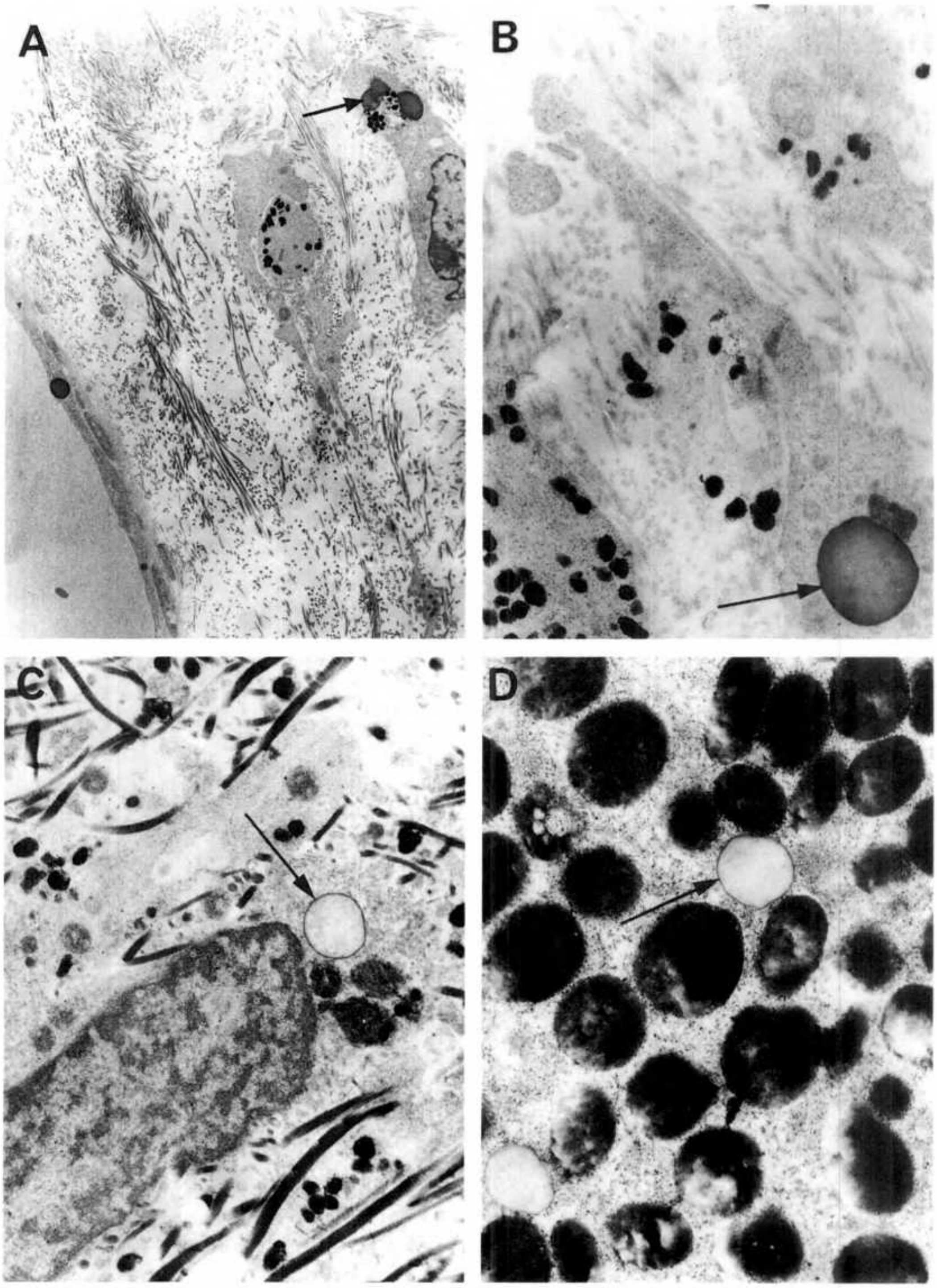

*Figure 2:* A, B, C: *Lipid droplets within the iris stromal cells and pigment epithelial cells.* D: *These droplets are of similar size to the larger melanosomes of the IPE. (EM,* ×5200 (A), ×24 500 (B, C, D.)

ularly easily seen within the sphincter muscle, especially when the immunohistochemical stain with desmin antibodies was used (Fig 1). Unfortunately routine processing with toluene and alcohols removes lipid, and, though histochemical techniques, such as Nile blue sulphate and Sudan III and black were employed, unsurprisingly no specific staining was recordable. The electron microscopy of post-fixation osmified tissue confirmed lipid deposition in the anterior border cells and stromal cells (Fig 2A, B, C). Similar lipid was shown among the melanosomes of the iris pigment epithelium (IPE) (Fig 2D), a site at which no previous workers had demonstrated such abnormal lipid droplets, though ciliary body and retinal pigment epithelial deposits have been shown.[6] The deposits of fat within these IPE cells were of similar size to the larger melanosomes found within the pigment epithelium (Fig 2D). As it could be supposed that such lipid deposits were secondary to cataract formation, a further review was undertaken of a series of iris biopsies from patients with Fuchs's heterochromic cyclitis with cataract and their controls, five of each. These 10 samples were previously[7] shown to have pigment epithelial cells covering a total of 53 grid squares, and a mean of 221 melanosomal areas were counted, per case, necessitating examination of many more. In this series no similar lipid inclusions to those seen in the Refsum's case were seen, though some of the control patients were noted to

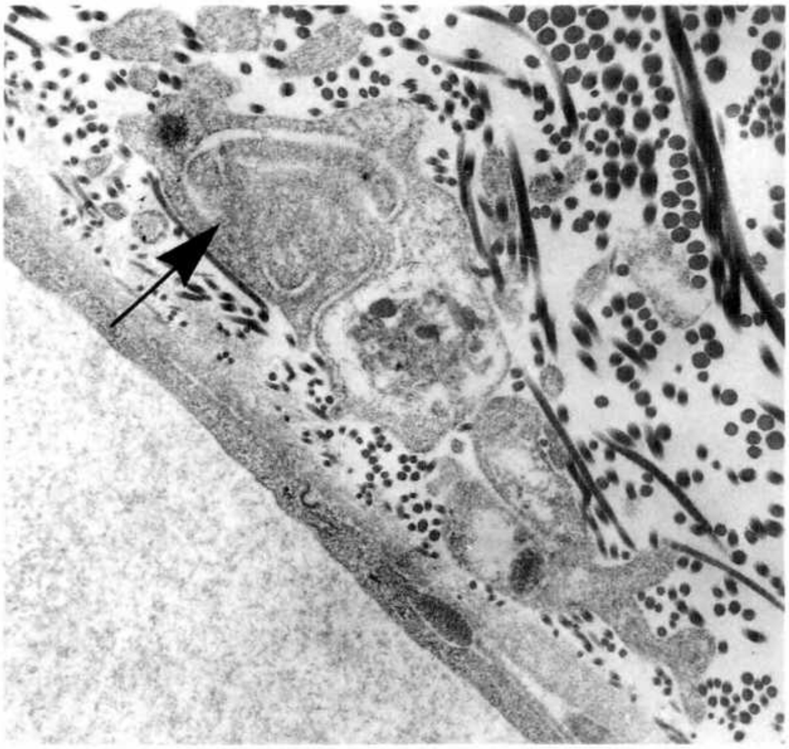

*Figure 3: Swollen and damaged unmyelinated axon lying within iris stroma, close to the sphincter. (EM, ×26 000.)*

have the intragranular vacuoles illustrated in Zinn's classic paper on the melanosomes of the iris.[8]

Axonal damage was seen within an unmyelinated nerve fibre (Fig 3) lying close to the anterior border, and fixation appeared adequate, with organelle preservation elsewhere, so that this appearance is unlikely to be artefactual. Such myxoid damage is usually associated with myelinated nerve fibres in other sites in the body in Refsum's disease, but no myelin figures were seen in this biopsy.

## Discussion

This demonstration of lipid droplets in the iris pigment epithelium shows lipid can be deposited in any part of the layer of pigment epithelium derived from neuroectoderm. Although the role of the RPE as a phagocytic cell tissue devouring effete rod outer segments is incontestable, it is not usual to ascribe this function to the pigment epithelia of the ciliary body and iris. The effects of accumulation of phytanic acid residues in nervous tissues may be primary, as is thought to be the case in myelin synthesis[9] with incorporation of a 'thorny' molecule instead of straight chain fatty acids. A similar mechanism may occur in the retina in membrane lipids, with consequent low lineoleate levels, known to influence electroretinograms.[10] The accumulation in pigment epithelia might be unrelated to the primary disorder or secondary effect which produces a clinical pattern similar to classical retinitis pigmentosa.

The ocular effects of this disease may therefore be primary leading to ptosis, miosis, ophthalmoplegia, and retinal malfunction, or secondary with further retinal damage due to RPE disease. Cataract may also be secondary to the accumulation of lipid within the lens epithelium itself or to disruption of the function of the ciliary body, and physical disruption is seen in glaucomatous eyes.

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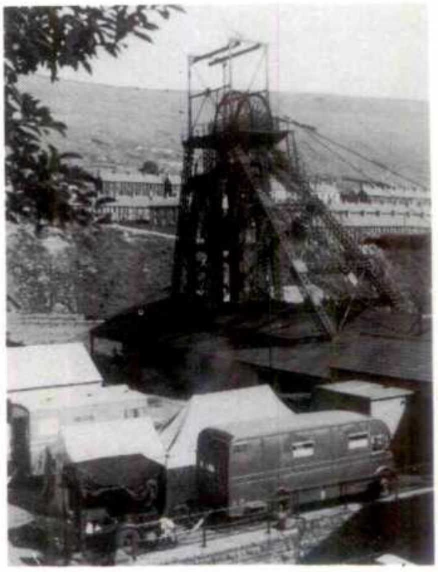

*Crown copyright*
The x-ray service of the Medical Research Council's Pneumoconiosis Research Unit visiting Tylorstown pithead in 1950.

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# Mucinous adenocarcinoma metastatic to the iris, ciliary body, and choroid

Wolfgang E Lieb, Jerry A Shields, Carol L Shields, George L Spaeth

## Abstract

**A 67-year-old woman presented with signs of severe intraocular inflammation and secondary glaucoma. The initial diagnosis was uveitis, and an anterior chamber paracentesis with cytological study of the aspirate failed to establish an aetiological diagnosis. After three trabeculectomies had failed to control the intraocular pressure, the blind eye was enucleated. On histopathological examination a mucinous adenocarcinoma was found to cover diffusely the iris surface and to involve the ciliary body and peripheral choroid. The patient subsequently developed evidence of widespread metastatic disease and died shortly thereafter. Although a primary tumour was never found, histochemical and immunohistochemical studies of the enucleated eye suggested that the lesion originated in the gastrointestinal tract. In cases of intractable glaucoma and anterior chamber inflammation, metastatic carcinoma should be included in the differential diagnosis, and efforts should be made to substantiate the diagnosis by a systemic examination or a biopsy.**

The commonest primary tumours to metastasise to the anterior uvea are breast, lung, and gastrointestinal tract carcinomas.[1-5] Rare tumours such as bronchial carcinoid, renal cell carcinoma, and squamous cell carcinoma of the cervix have been reported to metastasise to the anterior uvea.[6-10] However, in 9%[4] to 18%[2] of cases the primary tumour location is unknown despite extensive investigation.

Most metastatic carcinomas occur in the posterior choroid, and only 5%[1 4] to 11%[2] occur in the iris and/or ciliary body. Metastatic tumours to the anterior segment often present as solitary or multiple nodules on the iris or in the anterior chamber angle, with a diffuse shedding of cells into the anterior chamber simulating a severe anterior uveitis.[11-14] Metastatic tumours to the iris present with glaucoma in 7% of cases and later develop increased intraocular pressure in about half the cases.[3 15] We report a case of a metastatic carcinoma to the anterior segment of the eye that simulated uveitis and produced severe secondary glaucoma.

## Case report

In December 1984 a 67-year-old woman presented with an inflamed left eye. She was found to have an 'idiopathic iritis' and was treated with topical corticosteroids. Several weeks later she developed an intraocular pressure of 62 mmHg in the left eye. The glaucoma did not respond to conventional therapy, and the patient subsequently underwent trabeculectomy in March 1985. This procedure failed to control the elevated intraocular pressure in her left eye.

The patient was seen in consultation at another hospital in June 1985. The right eye was entirely normal. The intraocular pressures were 15 mmHg in the right eye and 40 mmHg in the left. The cornea was diffusely oedematous. Unusual translucent material was present on the anterior iris surface near the iridectomy site. A second trabeculectomy was performed during which translucent material was removed from the anterior chamber. Histological examination of the material disclosed fibrinous strands with acute inflammatory cells and macrophages. No bacteria, fungi, or malignant cells were found.

Despite the two prior trabeculectomies the patient continued to have a painful left eye with a raised intraocular pressure and was sent for further examination to the Glaucoma Service of Wills Eye Hospital. The intraocular pressures could not be controlled by conservative medical measures such as oral carbonic anhydrase inhibitors, β blockers, or topical corticosteroids. Cyclocryotherapy to 180° of the ciliary body was performed. Despite frequent topical corticosteroid therapy the anterior chamber inflammation could not be controlled. Postoperatively ultrasonography demonstrated inferonasal and inferotemporal choroidal detachments. Although the intraocular pressure was relatively well controlled, white debris continued to accumulate in the anterior chamber. An intraocular tumour was suspected, and the patient was referred to the Ocular Oncology Service at Wills Eye Hospital.

The patient had a history of a breast biopsy for a mass that had proved to be benign. There was no history of cancer. Visual acuity was 6/9 in the right eye and light perception in the left. Applanation intraocular pressures were 7 mmHg in the right eye and 13 mmHg in the left eye. The right eye was entirely normal. The left eye had a clear cornea and mild conjunctival injection. In the anterior chamber a diaphanous yellowish white material covered most of the anterior iris surface, and a moderate amount of cell material and flare were noted as well as a small hyphaema (Fig 1). There were no nodules in the iris or anterior chamber angle. The fundus could not be visualised because of the anterior chamber reaction and posterior synechiae.

The chronically inflamed, blind painful eye was enucleated in October 1985.

### MACROSCOPIC EXAMINATION

The specimen consisted of a soft left eye measuring 24×24×24 mm, with a short section of optic nerve attached. The cornea was clear and

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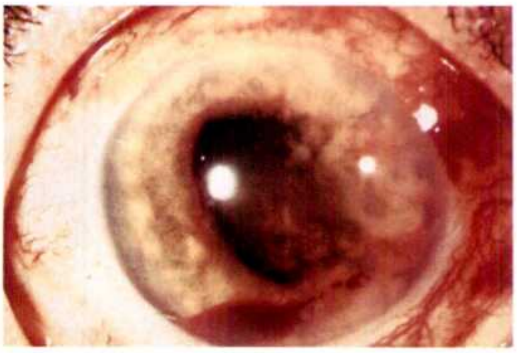

*Figure 1: Slit-lamp photograph of the anterior segment after a repeated trabeculectomy. There is a small hyphaema inferiorly. Nasally white fluffy material can be seen.*

measured 12·5×11·5 mm. The anterior chamber was almost completely filled with a fluffy white material (Fig 2). There was good transillumination, with no shadows seen.

The eye was opened vertically to include the prior iridectomy sites. On opening the globe the peripheral choroid and ciliary body were found to be thickened superiorly and covered with white material. There was also condensation of the vitreous in a funnel shaped pattern from the disc to the posterior surface of the lens.

MICROSCOPIC EXAMINATION

The cornea appeared normal except in its inferior part, where a layer of cuboidal cells was growing on to its posterior surface (Figs 3, 4). The cells had vacuolar cytoplasm and rather large atypical nuclei. This monolayer of cells grew along the surface of all structures in the anterior chamber and covered most of the trabecular meshwork. It reflected over the anterior iris surface where it assumed a papillary frond pattern (Fig 5). In some sections these cells grew around the pupillary margin on to the posterior surface of the iris and extended back to the pars plicata and the pars plana. In the ciliary body the mucin-producing cells formed small cysts containing mucinous material. In the anterior part of the choroid tumour cells were also seen forming duct-like structures with a central area of mucin. The remainder of the choroid, retina, and sclera was normal. The mucinous material stained positive with Alcian blue and was resistant to hyaluronidase. The material also stained positive with periodic acid Schiff and mucicarmine stains. Immunoperoxidase stains for carcinoembryonic antigen (CEA) were highly positive, suggesting that the primary tumour probably originated from the gastrointestinal tract.

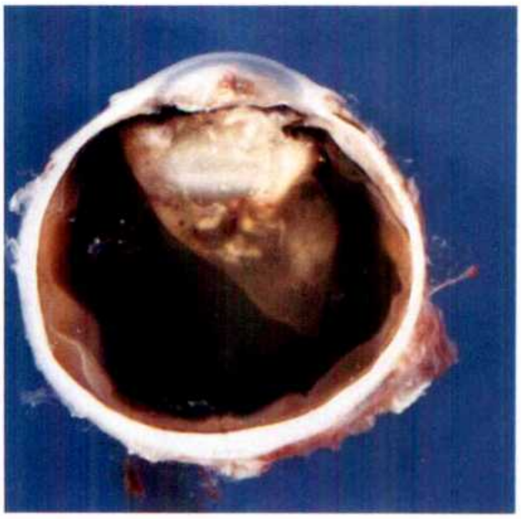

*Figure 2: Gross specimen shows white material and haemorrhage in the anterior chamber, a dense cataract, thickening of the ciliary body, and vitreous haemorrhage.*

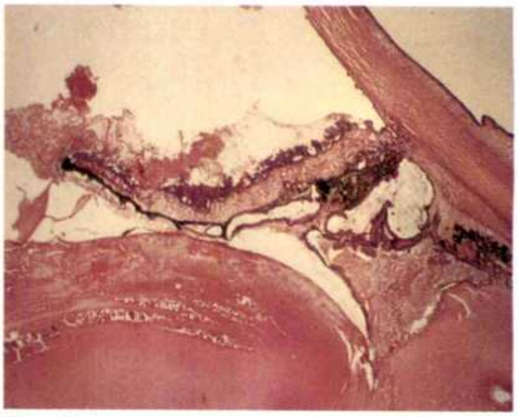

*Figure 3: Low-power photomicrograph showing parts of the anterior segment. There is a monolayer of cells growing on the back surface of the cornea, covering the anterior chamber angle, the anterior and posterior iris surface, and extending up to the pars plana. Posterior synechiae are present. (Haematoxylin-eosin, ×5.)*

Subsequently the patient underwent a complete evaluation for a primary malignancy. The results of the physical examination, including a breast examination, computed tomography of the head and abdomen, upper and lower gastrointestinal (GI) tract, proctoscopy, liver function studies, electrolytes, and complete blood count were normal. The only abnormality found was on the computed tomograph of the chest, in which a small pleural effusion and two pleural nodules were discovered. Aspiration of the pleural fluid revealed mucin producing adenocarcinoma cells with a high CEA level of 390 ng/ml (normal <5·0 ng/ml).

Owing to these findings the patient was reexamined for a primary tumour in the gastrointestinal tract, but none was found. She died six months later of pulmonary and cardiac failure secondary to widespread metastases. Permission for a necropsy was not granted.

## Discussion

Metastatic tumours to the eye are probably the commonest intraocular malignant tumours of adults. As has been shown in several series, they most commonly involve the posterior choroid.[1-4] Ophthalmological studies do not reflect the true incidence of these tumours because many metastases are never clinically discovered owing to their occurrence in patients with end stage disease, who do not undergo ocular examination.

Metastatic tumours to the iris and ciliary body may simulate an inflammatory process. In one series 10 out of 26 patients with metastases to the anterior segment presented with uveitis.[3] Anterior segment metastasis led to secondary glaucoma in 56%, and many of these cases underwent antiglaucomatous surgery.[3] The mechanism of the glaucoma in these cases is often two-fold. Besides the thin sheet of tumour cells covering the surface of the iris, the anterior chamber angle, and the posterior surface of the cornea, the production of mucus leads to a

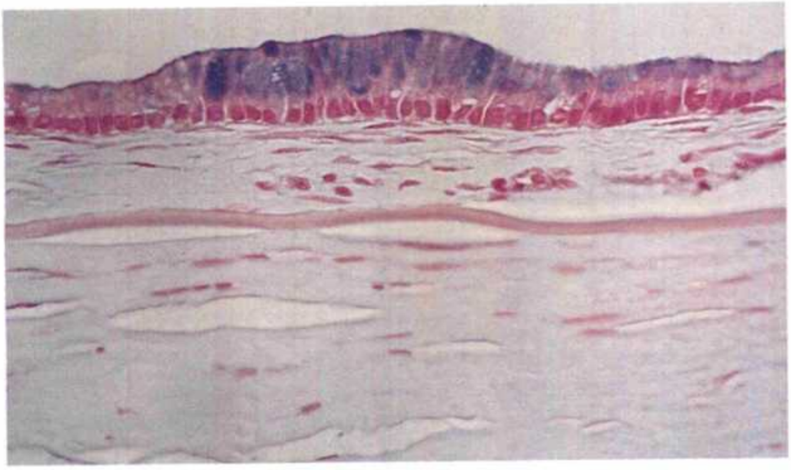

*Figure 4: high-power photomicrograph showing single layer of tumour cells forming a retrocorneal membrane and covering the peripheral cornea. (Alcian blue, × 150.)*

'mucogenic glaucoma'.[16] In some instances tumour induced iris neovascularisation can cause occlusion of the anterior chamber angle and increase of intraocular pressure. In a few cases the diagnosis was made clinically or by cytological examination of the specimen from anterior chamber paracentesis.[17-19] The majority of anterior segment metastases were diagnosed after enucleation for severe late complications of inflammation and secondary glaucoma, as occurred in our case. In several cases an aqueous specimen showed only a non-specific inflammatory reaction. However, since a large number of primary tumours that arise from the lung, breast, or gastrointestinal system produce CEA, measuring the serum level and levels of this antigen in the aqueous should be considered more often.[17 20-22]

In our specimen the carcinoma cells covering the anterior and posterior iris surface stained positive for CEA. This, in combination with the excessive mucin production and the papillary frond-like pattern, suggested the gastrointestinal tract as the most likely site of the primary tumour. A similar case with the primary carcinoma located in the caecum has been reported.[1]

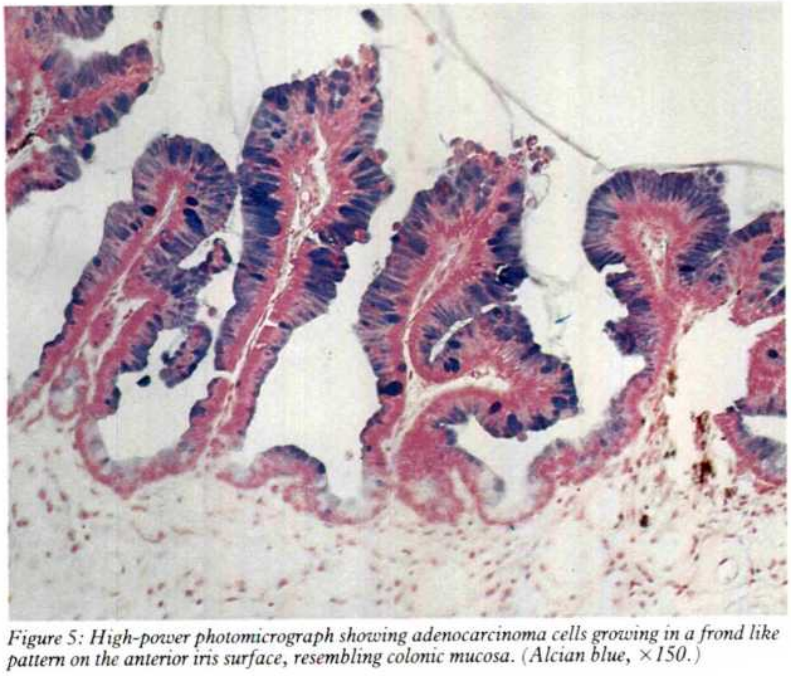

*Figure 5: High-power photomicrograph showing adenocarcinoma cells growing in a frond like pattern on the anterior iris surface, resembling colonic mucosa. (Alcian blue, × 150.)*

Several conditions should be included in the differential diagnosis of metastatic cancer to the iris and ciliary body. They include iris melanoma, adenoma of the ciliary pigment epithelium, and granulomatous uveitis. In contrast to amelanotic melanomas of the iris or ciliary body, iris metastases are generally more gelatinous, friable, and yellow. A metastasis may not present as a solid tumour nodule but rather as a diffuse sheath of cells covering the anterior iris surface. Only rarely do metastases infiltrate the deep iris stroma or break through the iris pigment epithelium into the posterior chamber. Two-thirds of all uveal metastases are purely cellular and do not have stroma vessels that could be demonstrated on biomicroscopy or fluorescein angiography.[23]

Primary adenomas and adenocarcinomas of the non-pigmented ciliary epithelium are extremely rare, and metastases have not been known to occur.[24 25] As Jakobiec *et al*[26] have pointed out, primary ciliary mucinous tumours tend to grow in strings and garlands and do not form complete lumina.

Iris metastases can seed cells into the anterior chamber forming a tumour-induced pseudohypopyon.[1] Other lesions which may be confused with anterior segment metastases include granulomatous uveitis (sarcoidosis or syphilis) and retained foreign bodies. The examination should be directed to exclude these lesions.

In cases of intractable glaucoma with severe persistent anterior segment inflammation a complete systemic examination should be undertaken to exclude a primary malignancy. If that shows nothing, an anterior chamber aspirate and/or a peripheral iridectomy may be performed at the time of the filtering procedure and sent for histological examination. If the diagnosis of a mucin-producing tumour is made, a distant primary tumour should be suspected, and a more extensive diagnostic examination should be undertaken. If no primary tumour is found and the patient is systemically well, then radiotherapy to the eye should be administered, approximately 3000 cGy–4000 cGy being given.[27] If a primary tumour is found, ocular radiotherapy may be withheld until a response to chemotherapy or hormonal therapy is assessed.[28]

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# Early diagnosis of the retinopathy of incontinentia pigmenti: successful treatment by cryotherapy

J Rahi, J Hungerford

## Abstract

**Prospective examination of the ocular fundi was carried out in the newborn female sibling of a girl with incontinentia pigmenti and bilateral retinopathy. At age 3 months the new baby's peripheral retina was found to be avascular in both eyes. At age 2 years progressive vascular proliferation at the watershed area between normal and abnormal retina led to bilateral vitreous haemorrhage. The new vessel tufts promptly regressed when the avascular area in each eye was treated by single-freeze cryotherapy and the blood in the vitreous absorbed. Cicatricial retinopathy was thereby prevented. Prospective retinal examination of newborn female siblings of children with incontinentia pigmenti is advised, with early cryotherapy recommended if progressive neovascularisation is detected.**

Incontinentia pigmenti is a rare familial syndrome of ectodermal and mesodermal dysplasia. In 1926 Bloch[1] described a case of an 18-month-old girl referred to him with a diagnosis of glioma with retinal detachment for his opinion on a patchy pigmented rash. A later case report by Sulzberger[2] added the suggestion that this was part of a familial syndrome of ectodermal defects.

The cutaneous manifestations may display three successive stages. The first is an erythematous vesicular rash associated with eosinophilia. Subsequently, verrucous lesions may occur and finally the characteristic rash on trunk and extremities, comprising brown splashes, streaks, or whorls of pigmentation. Pigmented lesions may occur without the preceding phases.

Some cutaneous features are usually present at birth. Histological examination of the pigmented lesions shows degeneration and depigmentation of the basal layer of the epidermis associated with numerous melanin laden macrophages and free melanin granules in the dermis. This increased dermal melanin is believed to originate in the basal epidermis and provided Bloch with a descriptive name for the condition.

Associated anomalies occur in 80%[3] of cases and include abnormalities of the central nervous system – for example, microcephaly and motor disturbances; dental, bony, hair, and cardiac anomalies have all been reported.

Protean ocular abnormalities occur in up to 35% of cases.[4] Most result in severe visual handicap. Typically a retrolental mass containing detached dysplastic retina[5] is seen at the time of diagnosis. In 15 to 40% of cases[6] there is a familial occurrence with an obvious female preponderance. The current view[7] is of an X-linked dominant inheritance which is lethal in the male fetus.

This paper describes the ocular findings in two sisters. The older girl, known to have neurodevelopmental delay and abnormal skin pigmentation consistent with incontinentia pigmenti, presented with bilateral ocular disease with an end-stage retrolental mass in one eye. Examination of the younger child was prompted by these eye findings and allowed early diagnosis of the retinopathy of incontinentia pigmenti and subsequent successful treatment.

## Case reports

### CASE 1

This girl presented in October 1985 at age 7 years with a three-week history of bilateral leucoria noted by the parents. She had been born at term after a normal pregnancy and delivery with a birth weight of 2·9 kg. There were no neonatal problems. From 8 months of age moderate developmental delay with microcephaly and abnormal involuntary movements were noted. A single patch of altered skin pigmentation was present on her left leg. She was the sixth of seven children born to Asian parents who were first cousins. Both parents were normal, as were the older five children, two boys and three girls. There were numerous consanguineous marriages in the family.

At presentation the following abnormal features were found in the left eye: a shallow anterior chamber, raised intraocular pressure, ectropion uveae, and complete fibrovascular retrolental membrane representing dysplastic retina. The right fundus showed a temporal membrane with dragging of the optic disc. Telangiectatic vessels were seen temporally associated with the membrane (Fig 1). At the time of presentation, the mother was near term in her seventh pregnancy and the parents were encouraged to attend for early ocular examination of the newborn baby.

### CASE 2

The seventh child was 3 months old when she was first seen in February 1986. At this time there were no general medical problems. She had been born at term after a normal pregnancy and delivery with a birth weight of 2·95 kg.

The first ocular examination showed the temporal peripheral retina to be somewhat avascular, with microvascular abnormalities at the watershed area between normal and abnormal retina in both eyes. These retinal findings remained unchanged until 2 years of

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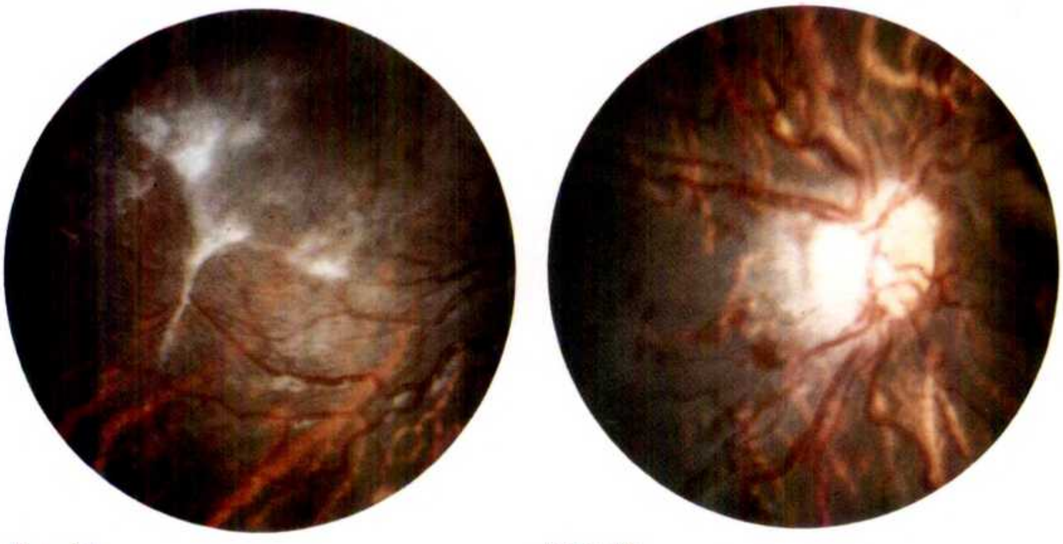

Figure 1A Figure 1B

*Figure 1: Case 1. A: Fundus photograph of the temporal periphery of the right eye showing a fibrovascular membrane. B: dragging of the optic disc in the same eye in association with telangiectatic retinal vessels and the temporal membrane.*

age. At this time there was evidence of progression of the vascular proliferation at the margins of the avascular retinal zone, with vitreous haemorrhage in both eyes. It was considered advisable to attempt treatment by cryotherapy of the avascular retina (Fig 2). After single freeze cryotherapy of the avascular retina in the right eye bleeding promptly ceased and the new vessel tufts disappeared. Meantime the changes progressed in the left eye but promptly regressed when this eye was similarly treated. There has been no regrowth of new vessels during follow-up of more than 18 months. There is minimal retinal traction, and the patient appears to have normal sight.

Since the initial ocular examination this patient has been found to have microcephaly and abnormal motor development. The diagnosis of incontinentia pigmenti has been confirmed by biopsy of pigmented lesions on the trunk.

## Discussion

A review by François[8] of the retinal changes seen in incontinentia pigmenti describes the many abnormalities which have been reported, including retinal pigment epithelium abnormalities, haemorrhagic and pigmentary retinitis, retinal dysplasia, glial strands, retinal detachment, and optic atrophy. He concludes that they are all probably consequent upon retinal vascular changes characterised by 'ectatic veins, formation of rete mirabile and pathological venous anastomosis', and that these are the basis of the retrolental mass seen in so many cases.

The findings of Watzke *et al*[9] and Nishimura *et al*[10] are consistent with our findings of the early retinal changes, and their fluorescein angiograms confirmed absence of perfusion in the areas of temporal peripheral retina beyond the zones of leaky anastomotic vessels and associated neovascularisation.

Nishimura and coworkers have described one case in which progression of vascular proliferation was arrested by photocoagulation but useful vision was not preserved because of optic atrophy and pigmentary macular change. Brown's report[11] of a child followed up from the first week of life showed failure of attempted treatment with ACTH and concurred with that of François in describing pseudoglioma as the end-stage of the observed retinal vascular changes. In this context it is postulated that a retinal angiogenesis factor stimulates the neovascularisation process.[12] Although the precise nature of such a factor is unknown, it is likely to be one of the several recently described by Folkman.[13]

The degree of retinal traction produced by the retinopathy of incontinentia pigmenti commonly differs between the two eyes, as illustrated by case 1 of the present report. The retinopathy of incontinentia pigmenti is similar in this respect to that of prematurity (ROP). As with ROP, progression of incontinentia pigmenti retinopathy ultimately slows or ceases without treatment, and it must be questioned whether the

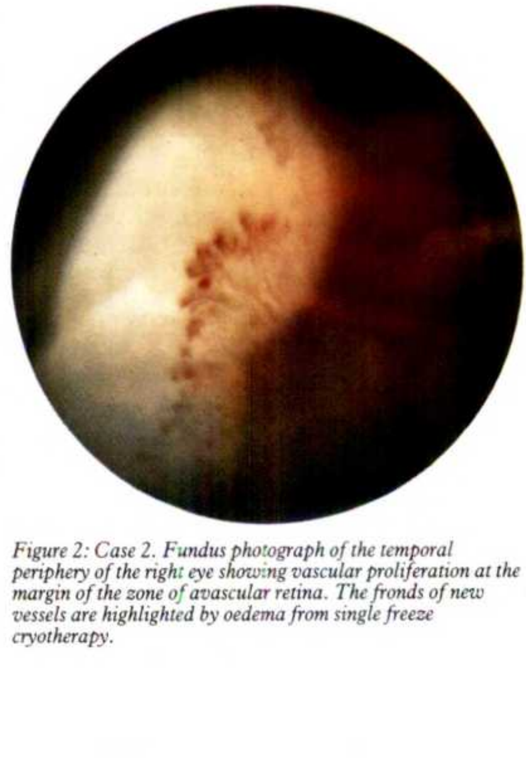

*Figure 2: Case 2. Fundus photograph of the temporal periphery of the right eye showing vascular proliferation at the margin of the zone of avascular retina. The fronds of new vessels are highlighted by oedema from single freeze cryotherapy.*

arrest of progress in case 2 was the result of cryotherapy or whether it occurred spontaneously. The rapid disappearance of new vessels and haemorrhage after cryotherapy in the first treated eye coincided with continued deterioration of the fellow eye, which was in turn rapidly reversed by treatment. These features and the ultimate lack of retinal traction compared with that seen in the sibling are compelling reasons to count case 2 as a treatment success.

As for ROP, early detection of new vessels is of paramount importance in incontinentia pigmenti retinopathy. If progressive neovascularisation threatens cicatricial retinopathy, treatment must be instituted early if it is to prevent retinal detachment. Experience from the cases reported indicates that the visual deficit of incontinentia pigmenti may be limited if female siblings of affected children are screened. We advise examination within a month of birth and repeat examinations at three-month intervals, even if there is no extraocular evidence of incontinentia pigmenti. If there are no retinal signs of the disease by 1 year of age, it is unlikely to develop later. Examination may need to be more frequent if retinal ischaemia and neovascularisation are detected, and treatment must be instituted at the first signs of progression.

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# Traumatic transconjunctival orbital emphysema

Edward M Stroh, Paul T Finger

### Abstract
**Orbital emphysema can be produced by transconjunctival migration of air from a high pressure airgun. In an industrial accident an 8 mm conjunctival laceration was produced in the superior fornix which acted as a portal of entry for air into the subconjunctival, subcutaneous, and retrobulbar spaces. Computed tomography revealed no evidence of orbital fracture and showed that traumatic orbital emphysema occurred without a broken orbital bone.**

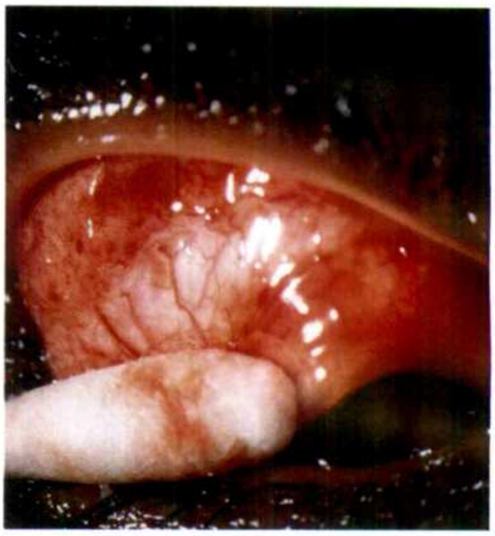
*Figure 2: An 8 mm conjunctival laceration is found in the region of the superior fornix.*

Traumatic orbital emphysema is usually the result of a fracture of the lamina papyracea or maxillary roof allowing air to pass from the sinuses into the orbit.[1-3] Although orbital emphysema may follow violent nose blowing, sneezing, or infection, there is usually a history of antecedent trauma.[4-7] The diagnosis is made when palpation of the eyelids produces pathognomonic crackling or crepitation, with radiological confirmation of orbital fracture. With computed tomography orbital fractures can be demonstrated in over 95% of cases.[8] We present a rare cause of orbital emphysema.

### Case report
A 34-year-old automobile mechanic accidentally directed a compressed airgun which delivered 100–120 pounds per square inch (psi) (690–830 kN/m$^2$) toward his right eye. His mouth and nose were protected by a face mask, but his eyes were unshielded. He presented with a foreign body sensation and swelling of the skin of his right eyelid.

Ophthalmic examination revealed a visual acuity of 20/20 in each eye, normal pupillary reactions, and full ocular motility. Hertel exophthalmometry readings were symmetrical at 21 in each eye, with a base diameter of 98 mm. External palpation of the right upper and lower lid and left lower lid revealed crepitus. No evidence of skin laceration was noted over either eye. Applanation tensions of 13 mmHg in each eye were recorded. Slit-lamp biomicroscopy was significant for a linear corneal abrasion and subconjunctival bubbles in the right eye, with no evidence of anterior segment inflammation or haemorrhage (Fig 1). On double eversion of the right upper lid with retraction of the conjunctiva an 8 mm conjunctival laceration was found (Fig 2). The results of indirect ophthalmoscopy were within normal limits in both eyes.

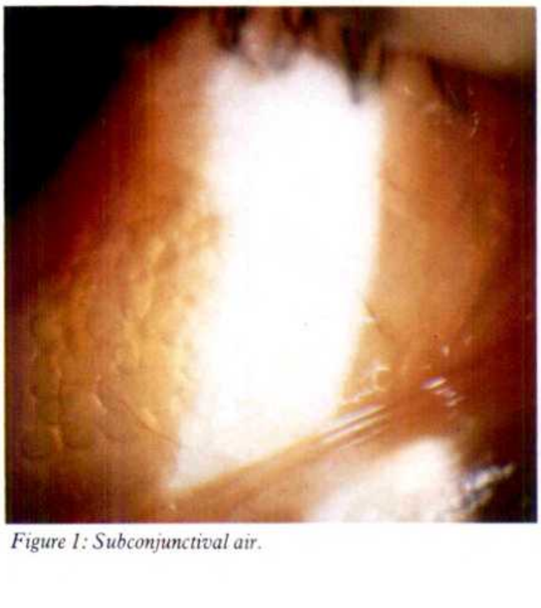
*Figure 1: Subconjunctival air.*

Computed tomography showed subcutaneous radiolucencies consistent with air within preseptal tissues and retro-orbital lucencies consistent with orbital emphysema (Fig 3). No air-fluid levels were noted in the sinuses, nor were fractures of the orbital bones noted on 2 mm axial and coronal sections.

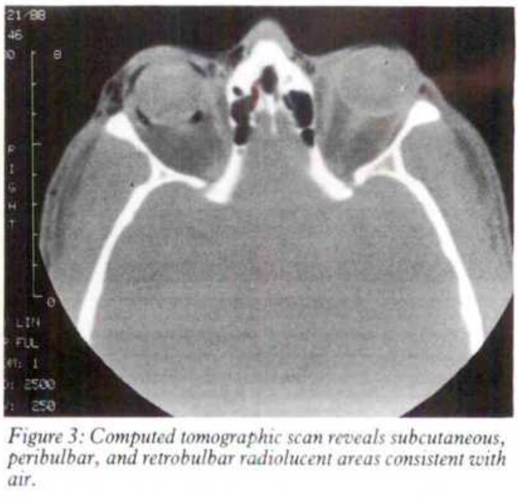

*Figure 3: Computed tomographic scan reveals subcutaneous, peribulbar, and retrobulbar radiolucent areas consistent with air.*

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Our patient was put on erythromycin ointment every six hours and improved within 24 hours. One month after treatment all evidence of trauma had resolved.

## Discussion

Orbital emphysema most commonly results from orbital wall fractures. In 20 cases of traumatic orbital emphysema described by Lloyd all were associated with fractures of the bony walls of the orbit as diagnosed by *x*-rays.[1] We found six cases of orbital emphysema caused by air blast trauma.[9-14]

In our case we used computed tomography to examine the state of the orbital bones and periorbital sinuses, to observe the presence and location of orbital air and the integrity of the globe, and to rule out the presence of solid orbital foreign bodies. This case also differs from others in that the patient did not develop serious sequelae such as glaucoma, hyphaema, uveitis, or optic neuropathy. There was also no evidence of intracranial extension of the air 'foreign body'. In fact this case demonstrates that air blast ocular injuries do not necessarily carry a poor ocular prognosis.

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# Glaucoma in siblings with Morquio syndrome

M Cahane, G Treister, F A Abraham, S Melamed

**Abstract**

**Two cases of association between the Morquio Syndrome and glaucoma in one family are described. Possible role of Mucopolysaccharides acting in the anterior chamber angle is discussed.**

Morquio syndrome (mucopolysaccharidosis type 4) was first described in 1929.[1] It is an autosomal recessive error of metabolism in which keratan sulphate is usually excreted in the urine.[2-5] Deficient activity of the enzymes N-acetygalactosamine 6-sulphatase (Morquio type A), or acid-b-galactosidase (Morquio type B) has been reported in this disease.[5-8]

The syndrome is characterised by severe skeletal changes which include hypoplasia of the odontoid process, short neck, pectus carinatum, kyphoscoliosis, and dwarfism. There are also laxity of joints and characteristic roentgenographic findings.[2-4] Other manifestations include aortic regurgitation, thinness of tooth enamel, and neurosensory deafness.[2] The syndrome is distinguished from other mucopolysacharidoses by the absence of mental retardation.[2-4 9 10] Clinical findings develop in early childhood and are not apparent at birth.[2 9]

The most striking ocular finding is corneal stromal clouding, which is present in nearly all cases but may not be evident until adolescence.[2 3 6 9] Retinal involvement, slight scotopic impairment, and blurred discs have also been reported.[2 11]

Glaucoma is not considered to be part of the Morquio syndrome. We have found only one report of two brothers with bilateral buphthalmos,[12] and in another case extensive anomalies of mesodermal iris tissue were observed in the anterior chamber angle.[9]

In this report we describe an unusual case of two siblings (a brother and a sister), aged 35 and 36 years respectively, with Morquio syndrome and glaucoma.

## Case reports

### CASE 1

This was a 35-year-old man who was diagnosed many years ago as having Morquio syndrome. His 36-year-old sister has the same disease. Another brother died at the age of 22 and had Morquio syndrome. Both parents and another brother are healthy. Since childhood the patient has had corneal clouding in both eyes. Three years ago a high intraocular pressure (IOP) of 30 mmHg was measured in both eyes. Treatment with topical drops of 2% pilocarpine four times a day and later 1% epinephrine twice daily was given in both eyes. In the last year the IOP was not controlled despite the addition of 0·5% timolol maleate twice daily, and he was referred to our clinic for further evaluation.

On examination the patient's height was found to be 82 cm. He had kyphoscoliosis, a short neck, pectus carinatum, and laxity of joints.

The visual acuity was 20/100 in both eyes. Both corneas had hypoaesthesia and stromal clouding, more dense centrally. The stromal clouding contained a large number of small dust-like opacities. The IOP (under full topical treatment) was 31 mmHg in both eyes as measured both by Goldmann applanation and Schiøtz tonometry. The anterior chamber was deep and the iridocorneal angle was open, but the detailed structures could only be poorly visualised due to corneal haziness. The lens appeared clear, and the fundus could not be examined in detail. The axial length was 26·5 mm in the right eye and 27·0 mm in the left. Visual field testing showed generalised constriction in both eyes.

The electroretinogram (ERG), evoked by full field light flash stimulation, showed responses of normal amplitude and implicit times of both photopic and scotopic retinal mechamisms. The visual evoked potentials (VEP) showed normal stimulus propagation through the optic pathway. Colour vision was normal.

### CASE 2

This patient was a 36-year-old female, the sister of case 1. She also has Morquio syndrome, with severe dwarfism. She is known to have had corneal clouding in both eyes for many years.

A raised IOP in both eyes was found five years ago, and since then she has been treated with 1% epinephrine and 0·5% timolol meleate twice daily. She was referred to us for further evaluation of her ocular status.

On examination her height was found to be 75 cm. She had kyphoscoliosis, a short neck, pectus carinatum, and a cardiac murmur due to aortic regurgitation.

The visual acuity was 20/100 in both eyes. The IOP was 31 mmHg without treatment. Both corneas had hypoaesthesia and diffuse stromal clouding, containing numerous small dust-like opacities. The anterior chamber was deep, and gonioscopy revealed an open angle, but the details could not be examined owing to corneal opacity. The lens was clear in both eyes, and fundus examination was impeded by a hazy view. The axial length was 22·0 mm in the right eye and 21·1 mm in the left. No specific visual field defects other than generalised constriction of field were found.

The ERG recordings showed normal photopic and scotopic responses, and the VEP revealed normal conduction in the optic pathway. Colour vision was normal.

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## Discussion

In the mucopolysaccharidoses there is a deficiency in enzymes degrading mucopolysaccharides. Consequently mucopolysaccharides accumulate in various organs, including the corneal stroma. It is of interest that glaucoma has not been associated with these diseases, though one would expect to see more cases of glaucoma due to mucopolysaccharide accumulation in the trabecular meshwork. It is believed that proteoglycans in the trabecular meshwork contribute to the resistance of the aqueous outflow.[13] Knepper *et al*[14] have used selective glycose aminoglycans (GAGS) enzyme degradative procedures to identify GAGS in the trabecular meshwork of eyes with primary open-angle glaucoma. They found that hyaluronic acid was decreased, while chondroitin sulphate and GAG-enzyme resistant material were raised. Therefore it is suggested that accumulation of these materials is important in the pathogenesis of glaucoma.

Lack of glaucoma in most cases of mucopolysaccharidosis may be explained by the short life of these patients. In Morquio syndrome, however, the life span is longer, so that there is more time for the accummulation of mucopolysaccharides in the trabecular meshwork, resulting in glaucoma.

In this report we present two siblings with Morquio syndrome, with corneal stromal clouding and glaucoma. In contrast to patients with Morquio syndrome previously described in the ophthalmic literature, who are usually children or adolescents, our patients are older. It is possible that alterations of the metabolism of mucopolysaccharides affect the trabecular meshwork slowly, and so glaucoma appears at an older age.

We suggest therefore that patients with Morquio syndrome should be examined with special attention to detect signs of glaucoma, and topical treatment should be initiated if a raised intraocular pressure is found.

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# LETTERS TO THE EDITOR

## Treatment of developmental glaucoma

SIR,—We wish to report on a patient with developmental glaucoma whose worse eye, previously controlled by surgical goniotomy, subsequently became uncontrolled and was further treated by Nd-YAG laser goniotomy with immediate improvement in pressure control.

On presentation at age 2 a boy with moderately severe cystic fibrosis was found to have an enlarged right cornea. At examination under sedation with methohexitone 20 mg the right cornea was found to have breaks in Descemet's membrane, and the intraocular pressures were 16 mmHg in the right eye and 12 mmHg in the left by applanation tonometry. Asymmetrical cupping of the optic discs was noted, with a ratio of 0·75 in the vertical meridian in the right eye and 0·4 in the left eye. The glaucomatous process at this stage was considered to be inactive.

Re-examination under sedation with methohexitone 30 mg 18 months later revealed intraocular pressures of 18 mmHg in the right eye and 12 mmHg in the left eye by applanation tonometry. The appearance of the optic discs was unchanged.

A year later the right intraocular pressure was found to be 30 mmHg by applanation tonometry performed without general anaesthesia or sedation. A month later under general anaesthesia the right intraocular pressure was 30 mmHg by applanation tonometry, the left being under 20 mmHg. The right horizontal corneal diameter was 13·75 mm, the left being 12·75 mm. A right inferior quadrant goniotomy was performed.

Subsequently the intraocular pressures remained under 21 mmHg without topical treatment for 14 months, but the pressure in the right eye then rose to 24 mmHg, with an increase in the cup disc ratio. It was impossible to obtain an accurate visual field in this child. Right gonioscopy at this time showed an open angle inferiorly, but the superior, nasal, and temporal quadrants were occluded by a membrane, iris processes extending to the anterior limit of the trabecular meshwork.

In view of his respiratory problems and good co-operation at age 6 it was decided to attempt Nd-YAG laser goniotomy under topical anaesthesia rather than institute medical antiglaucomatous treatment. A Lasag Topaz Nd-YAG laser was used with a Lasag CGA contact lens with the patient seated at the apparatus. Three clock hours of angle were opened by the application of 17×4 mJ single pulses to the anterior limit of the iris insertion. The iris was seen to fall away and the trabecular meshwork became visible in the treated area.

The procedure caused only very minimal haemorrhage in the angle. The following day the intraocular pressure in the right eye was 16 mmHg, and there were only a few inflammatory cells in the anterior chamber. No topical treatment was given subsequently.

Six weeks later the right intraocular pressure was 15 mmHg, at five months 18 mmHg, at eight months 20 mmHg, at 13 months 17 mmHg, and at 20 months 20 mmHg, all measured by applanation tonometry.

We feel that the short term results in our patient and those reported by Kitazawa *et al*[1–3] suggest that Nd-YAG laser goniotomy may be a real alternative to surgical goniotomy in the management of developmental glaucoma associated with simple trabecular dysgenesis. Kitazawa and colleagues' patients were aged 16 to 45 years. Our patient was aged 6, but was very co-operative, as is often the case in this situation.

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## More Healonid for your money

SIR,—Visco-elastic substances such as sodium hyaluronate (Healonid) have many applications in ophthalmic surgery in separating tissues and in protecting them from trauma. Healonid is supplied in prefilled disposable syringes delivering either 0·5 or 0·75 ml of a buffered solution of sodium hyaluronate. In many centres the high cost of Healonid is a factor which limits its use. We wish to report a simple method of obtaining additional Healonid from the prefilled syringe.

When the syringe is emptied by complete depression of the plunger, the dead space of the syringe and cannula contains 0·06 ml of Healonid, some of which can be extracted by removing the cannula from the syringe and attaching it to another syringe filled with air. The air can be expelled from this latter syringe by gentle pressure, which will flush the residual Healonid out of the dead space of the cannula, allowing it to be used by the surgeon in the same operative procedure. By so doing a further 0·03 ml of Healonid which would otherwise have been discarded can be obtained from the prefilled syringe. This represents over 5% of the initial volume of Healonid, and in our experience the use of this simple technique often prevents a second syringe of Healonid being opened at the end of a procedure for a final application – for example, to coat an intraocular lens – with considerable financial saving.

It is emphasised that this technique is advocated to obtain the additional Healonid from the prefilled syringe only for use during the same operation and not to be conserved for future use on another patient.

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## Epikeratophakia with biological adhesive

SIR,—The recent paper by Halliday on epikeratophakia reports two cases where he attempted unsuccessfully to fix the graft with glue.[1] It has been shown in experimental work that success in glueing epikeratophakia grafts with commercially prepared fibrinogen adhesive is dependent on modifications of the lenticule design and the operative technique,[2] which were not, however, used in his cases. Fibrinogen adhesive prepared from individual donors can also be effective in glueing experimental epikeratophakia grafts.[3] On the basis of these findings early clinical trials have demonstrated that epikeratophakia grafts can be successfully glued in humans with autologous fibrinogen, with graft retention in every case.[4] Not only does the glueing technique make the operation much simpler and quicker to perform but it may also improve the visual results by reducing the effect of variation in suture tension. It also obviates the need for suture removal, which in children may require a second anaesthetic.

It is hoped that the advantages of the use of adhesive will be demonstrated by the results from the prospective controlled trial recently approved to be carried out at St George's Hospital.

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# NOTE

## Nordic meeting

The XXX Nordic Ophthalmological Meeting will be held on 25–28 August 1991 at Helsinki, Finland. Further information from Dr Raine Mustonen, Department of Ophthalmology, University Central Hospital, Haartmaninkatu 4C, 00290 Helsinki, Finland.

# AJO

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